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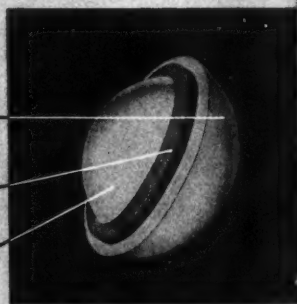
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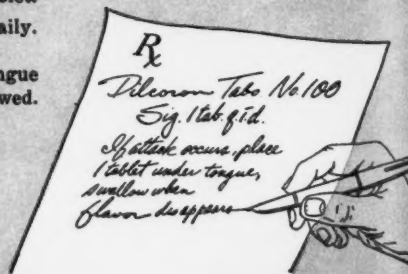
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## Editorial

### Current Status of Bretylium and Guanethidine as Antihypertensive Drugs

THE APPEARANCE of a new, effective antihypertensive drug no longer surprises physicians. They are now accustomed to treating hypertension, more or less effectively, because between 1950 and 1958, 4 types of antihypertensive drugs became available for clinical use. These drugs are by no means ideal, but they have been lifesaving in some patients with malignant hypertension or cardiac failure, and they have become progressively freer of side effects. Accordingly, physicians expect to see developed an antihypertensive drug that is effective in most patients, easy to administer, and without important side effects. These expectations will probably be fulfilled, but until then such optimism should not be allowed to dull critical analysis of new drugs as they become available.

Over a year ago bretylium and guanethidine were released for clinical trial as antihypertensive drugs with novel mechanisms of action.<sup>1,2</sup> Both interfere with sympathetic nerve function, either by depressing norepinephrine release or by depleting blood vessels and heart of this amine. Their antihypertensive effects are thought due to these actions. The advantage of these 2 drugs is that they suppress sympathetic function without causing parasympathetic blockade.

Drugs with such selective effects on the nervous system could have clear therapeutic

advantage. A brief look at the other 4 widely used agents reveals that, for the most part, they act through nervous mechanisms. In the case of the ganglion-blocking drugs, sympathetic vasomotor outflow is blocked at the ganglia; reserpine not only diminishes outflow from the central nervous system, but also depletes heart and blood vessels of norepinephrine; oral diuretics, at least in the early days of treatment, act predominantly through sympathetic pathways. Hydralazine, alone, does not seem to have a major nervous system action. We know that the sympathetic nervous system is concerned in the maintenance of arterial pressure. Whether this is greater than normal in most patients with hypertension is not known. Whatever the circumstance may be, ganglion-blocking agents lower blood pressure. Because they cause parasympathetic as well as sympathetic blockade, they can interfere seriously with function of the gastrointestinal and genitourinary tracts. This is their main disadvantage. Since both bretylium and guanethidine have the property of depressing only sympathetic function, they might well represent an advance in the therapy of hypertension.

Before any drug can be accepted as effectively antihypertensive, however, it must be shown to cause neither tolerance nor early or late incapacitating side effects. Further it must be determined whether the level of arterial pressure can be reduced sufficiently in order that the drug be classed as effectively antihypertensive. On this there apparently

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is no agreement. Some investigators emphasize orthostatic hypotension as the criterion for a good response; others, a reduction in mean arterial blood pressure of 20 mm. Hg or more. We insist that an effective drug lower pressure in both the supine and standing positions. This last opinion is based on experience with long-term treatment of malignant hypertension, which showed that those patients who achieved good control of supine arterial pressure lived longer than did those whose pressure was lowered only in the standing position.<sup>3</sup>

Both bretylium and guanethidine have been under clinical study for over a year and sufficient evidence has accumulated to show that bretylium has serious disadvantages and that guanethidine, although not ideal, is a potent drug of long-term effectiveness. Since both depress sympathetic function, both cause orthostatic hypotension, and this can occur without reduction in supine arterial pressure. This propensity indicates that neither drug can be used as casually as are reserpine and oral diuretics, and also that there may be some disagreement as to their effectiveness as antihypertensive agents. The first report on the use of bretylium emphasized orthostatic hypotension, indicating this as a measure of effectiveness.<sup>1</sup> Subsequent reports have been less enthusiastic.<sup>4, 5</sup> We have found that it causes primarily orthostatic hypotension and that when decreases in supine pressure are achieved, they are not usually maintained for more than a few weeks.<sup>6</sup> This indicates development of tolerance and is in accord with the experience of others.<sup>4, 5</sup> As yet no reports of tolerance to guanethidine have appeared nor has this been our experience in 16 months of use.<sup>7-9</sup> We find guanethidine to achieve sustained decreases of arterial pressure in both supine and standing positions.

Bretylium caused parotid pain in 10 of 13 patients whom we treated.<sup>6</sup> It appeared with the first few bites of food and usually disappeared if the patient could continue to eat; however, in a few the pain was so severe that they did not eat enough to maintain

body weight. Its cause is obscure; it is not due to obstruction of Stenson's ducts, and salivary production in response to citric acid has been found to be normal. The dose of bretylium given may influence the rapidity with which the pain develops after treatment is begun; we used 2 to 8 Gm. per day and observed onset of pain in the early weeks or months of treatment; others using smaller doses have not emphasized this side effect.<sup>4, 5</sup> Even after the drug has been discontinued for many weeks, the pain may persist. In this regard, it is interesting that this symptom has been reported in 1 patient with spontaneous orthostatic hypotension.<sup>10</sup>

Guanethidine's most frequent side effect is mild diarrhea. It usually responds to parasympathetic-blocking drugs and often lessens as treatment is continued. Occasionally reduction in drug dosage is necessary. It may result from autonomic imbalance of the intestinal tract, since suppression of sympathetic function would leave parasympathetic function unchecked.

Both bretylium and guanethidine represent a more specific therapeutic attack on that component of hypertension maintained by sympathetic vasomotor tone. After 16 months of study with guanethidine it is our opinion that it is a reasonably effective antihypertensive agent with minimal side effects. Bretylium has the disadvantage of more readily developing tolerance and in large doses, eliciting parotid pain of moderately severe grade.

IRVINE H. PAGE

HARRIET P. DUSTAN

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I am the last to deny medical science credit for remarkable achievement in the conquest of disease and for disinterested devotion to human betterment. Actually, I think that medicine is doing its job admirably if that job is conceived to be only the care of the human organism, taken "as is," and the remission of venial biological sins which are consequent upon civilized man's abuse of his bodily inheritance.

I appeal to medicine because it is the one branch of applied science which might be expected to realize not only that human behavior is a function of the human organism, but that all animal organisms exist and transmit their qualities through the mechanism of heredity. The fundamental principle of organic evolution is improvement or retrogression through the selection of inherited anatomical features and physiological functions. . . . Our entire system of education is upside down because it studies only human behavior and not the human organism; we know virtually nothing at all of the most vital factor in human evolution—human heredity.

I ask whether medical science is prepared to accept the responsibility for the reckless deterioration of human stock which it promotes by lavishing its skill and care upon the preservation of the unfit, when it takes no measures whatsoever for beginning the study of human inheritance by which alone permanent improvement of the species can be anticipated. I call upon this profession which is actually directing the course of human evolution downward to reflect upon the wages of biological sin.—EARNEST A. HOOTON. *Twilight of Man*. New York, G. P. Putnam, 1939, p. 304. (Submitted by H. M. Marvin, M.D.)

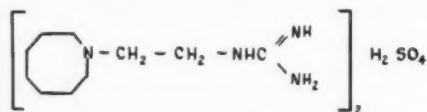
# Circulatory Effects of Guanethidine

## Clinical, Renal, and Cardiac Responses to Treatment with a Novel Antihypertensive Drug

By D. W. RICHARDSON, M.D., E. M. WYSO, M.D., J. H. MAGEE, M.D.,  
AND G. C. CAVELL, M.D.

**G**ANGLIONIC blockade, though an effective method of lowering blood pressure in hypertensive patients, is frequently accompanied by many unpleasant effects attributable to blockade of the parasympathetic nervous system. These side effects limit the reduction in blood pressure practicably attainable.<sup>1</sup>

The development of a new hypotensive agent that reduces sympathetic nervous discharge without inhibiting parasympathetic activity has provided a promising approach to the management of hypertensive vascular disease. This drug, which has the chemical structure shown below and the chemical title



2-(octahydro-1-azocinyl)-ethyl guanidine sulfate, has been assigned the generic name guanethidine.

### Pharmacology

Guanethidine, a synthetic antihypertensive agent developed by Ciba Pharmaceutical Products, Inc., was shown by Maxwell et al.<sup>2</sup> to cause marked and prolonged reduction of blood pressure in dogs with renal and neurogenic hypertension. With regard to its mechanism of action, the drug is thought to interfere with release of norepinephrine from sympathetic nerve endings. Evidence to support this mechanism is as follows: guanethidine produces marked and prolonged relaxation of the nictitating membranes of dogs and cats. This relaxation cannot be overcome by electric stim-

ulation of the preganglionic cervical sympathetic nerves, but it is readily reversed by infused norepinephrine. The drug does not interfere with transmission of impulses along preganglionic nerve fibers or across the superior cervical ganglion.<sup>2</sup> It seems reasonable to infer that the drug does not make effector cells unresponsive to the chemical mediator of neuro-effector activity, nor does it interfere with nerve or transganglionic transmission, but that it inhibits release of the mediator from sympathetic nerve endings.

In the early phases of its action, lasting 30 to 60 minutes, guanethidine demonstrates sympathomimetic effects such as contraction of the nictitating membrane and pilo-erection. These effects have suggested the possibility that guanethidine may release stores of the transmitter substance normally present in sympathetic nerves. This suggestion is supported by the observation of Sheppard<sup>3</sup> that the drug reduced catecholamine levels in the hearts and spleens of rats.

### Clinical Effects of Guanethidine

#### Reduction in Blood Pressure

Twenty-five male patients, hospitalized with severe hypertensive disease, have been treated with guanethidine\* for periods up to 6 months.<sup>4</sup> The drug was commonly given in doses of 150 to 200 mg. on the first day, half of this dose on the second day, and 25 to 75 mg. daily thereafter, the maintenance dose being adjusted to give maximum reduction in blood pressure without intolerable side effects. Striking reduction in pressure was achieved

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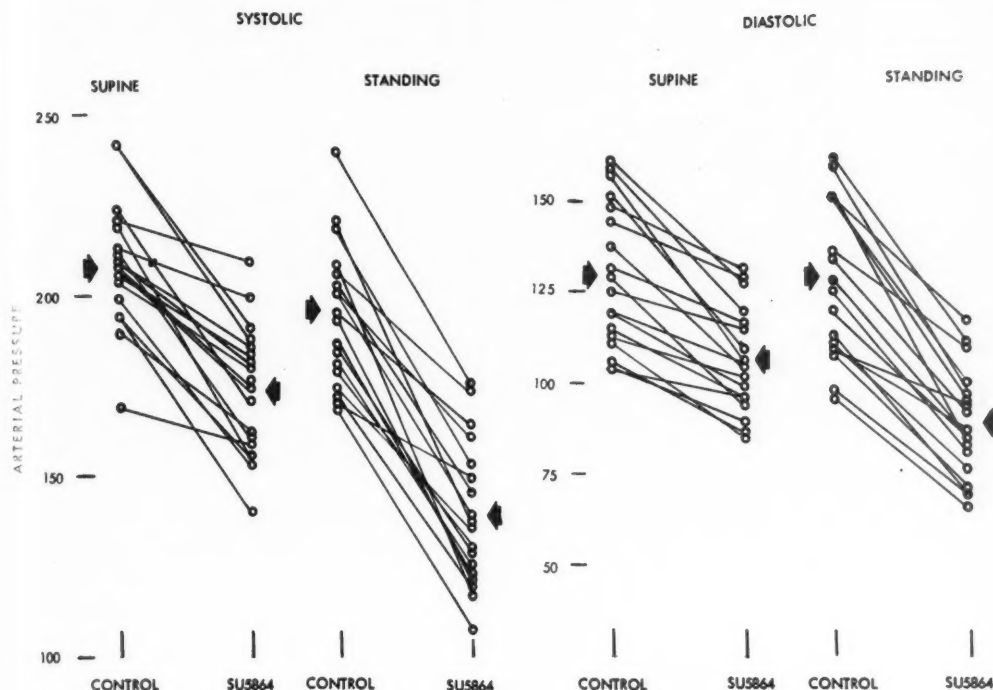


Figure 1

Blood pressure response to guanethidine. Control pressures are averages of 12 values recorded on each patient on the fourth through sixth hospital day. "SU 5864" values are averages of 20 pressures recorded in each patient on 5 consecutive days during maximum effect of the drug. Arrows indicate mean value in each vertical column.

in every case, was maximum within 48 to 72 hours after the beginning of treatment, and was maintained at lowest levels for 3 to 4 days after administration of the drug was stopped. Blood pressure gradually returned to pretreatment levels in 7 to 21 days following omission of the drug. Figure 1 shows consistent reduction in blood pressure observed in the first 18 patients treated. Similar results were noted in the remaining 7 patients. Standing pressures decreased more than supine values and pulse pressure decreased in the standing position. Diastolic pressure decreased an average of 23 mm. Hg supine and 45 mm. Hg standing.

Guanethidine has a "steep" dose-response relation, 25-mg. increments or decrements in maintenance dose frequently being accompanied by changes of 20 to 30 mm. in pressure.

Blood pressure can be reduced to extremely low levels in the standing position. Orthostatic dizziness or fainting occurred in 15 of the first 25 patients studied. Symptoms were relieved at once by lying down, and pressure rose to normal or high levels within 1 minute after resuming the supine position.

#### Side Effects

Orthostatic dizziness and fainting were the most common and troublesome untoward effects of the drug. The only "side-effect" commonly observed was mild diarrhea, 2 to 4 loose stools daily, which was poorly controlled by atropine, but easily controlled with paregoric. None of the parasympatholytic effects of ganglionic-blocking drugs, such as constipation, impairment of near vision, dry mouth, urinary retention, or impotence, was observed. Failure

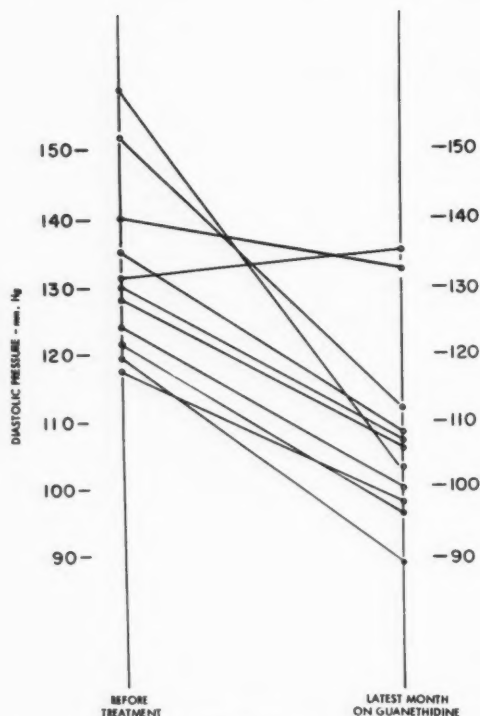


Figure 2

Maintenance of blood pressure reduction during long-term guanethidine therapy. Pretreatment pressures are derived as described in figure 1. Pressures during treatment are the averages of 60 values recorded by the patient twice daily at home during the latest month available.

of ejaculation without failure of erection occurred in 2 subjects.

Results similar to those presented above have been reported by Page and Dustan.<sup>5</sup>

#### Long-Term Administration

Eleven patients have been followed for 2 to 6 months after discharge from the hospital. These patients all had severe hypertensive disease (7 had grade 3 or 4 retinopathy, 11 had enlarged hearts, and 9 had diastolic pressures before treatment averaging more than 120 mm. Hg). They recorded their blood pressures twice daily in the sitting position at home. Average maintenance dose of guanethidine has been 50 mg. daily, though individual patients took from 25 to 300 mg. daily. As

shown in figure 2, satisfactory reduction in blood pressure occurred in 9 of the 11, and in 2 orthostatic dizziness prevented adequate control. No abnormalities occurred in repeated determinations of hematocrit, white blood cell count, serum bilirubin, serum glutamic oxalacetic acid transaminase or in urinalysis.

#### Circulatory Changes with Guanethidine

##### Cardiac Output

Measurements of cardiac output were made by the indicator-dilution technic, with a continuously recording densitometer (Colson), and injection of indocyanine green dye into an antecubital vein. Details of the technic and comparison of the peripheral injection site with central injection and with simultaneous direct Fick estimates of cardiac output have been presented previously.<sup>6</sup> Prior to treatment with guanethidine, 2 determinations of cardiac output in the supine position were followed by measurements made 1 and 5 minutes after tilting the head of the fluoroscope table up 40° from horizontal. When maximum reduction in pressure was achieved by guanethidine administration, usually 5 to 7 days later, duplicate determinations in the supine and 40° tilted position were repeated. Table 1 presents the average values of blood pressure, cardiac output, and calculated peripheral resistance that were observed. Blood pressure fell with guanethidine, mean pressure during treatment being 21 per cent lower in the supine position and 33 per cent lower in the standing posture. Cardiac output also fell, being reduced an average of 10 per cent in the lying and 33 per cent in the standing position, as compared with supine values before treatment.

Peripheral resistance, the quotient of mean arterial pressure divided by cardiac output, did not change greatly during the fall in blood pressure produced by guanethidine (fig. 3). During guanethidine treatment assumption of the semi-standing position reduced blood pressure 21 per cent without altering peripheral resistance. Though resistance was slightly (14 per cent) lower in the supine position during guanethidine administration than prior to

Table 1  
Effects of Guanethidine on the General Circulation

	Supine			40° Tilt		
	Off	On		Off	On	
Mean arterial blood pressure mm. Hg	(17)* 157 ± 24	(20) 126 ± 16†	(23)	150 ± 24	(21) 99 ± 22†	
Cardiac output L./min.	(21) 6.6 ± 1.7	(20) 5.9 ± 1.7	(23)	5.5 ± 1.8	(21) 4.4 ± 1.2‡	
Total peripheral resistance dynes cm. <sup>-2</sup> sec.	(21) 2144 ± 801	(20) 1846 ± 642	(23)	2450 ± 943	(21) 1875 ± 531‡	
Heart rate beats/min.	(21) 75	(20) 61	(23)	76	(21) 64	
Stroke volume ml./min.	(21) 91	(20) 98	(23)	72	(21) 72	

\*The numbers in parentheses are the number of determinations from which the mean values were calculated, and the results are reported as mean  $\pm$  1 standard deviation.

†Mean values that are significantly different from the control mean in the same position at the  $p < .01$  level.

‡Denotes differences significant at the  $p < .05$  level.

treatment, the difference was not statistically significant.

Insofar as the changes in calculated total peripheral resistance can be assumed to represent changes in the average caliber of arterioles,<sup>7</sup> it appears that reduction in blood pressure accompanying guanethidine administration is not brought about by relaxation of arteriolar constriction, since peripheral resistance decreased only slightly. Thus guanethidine, like ganglionic-blocking drugs<sup>8,9</sup> presumably lowers blood pressure by reduction in cardiac output, possibly by inhibition of sympathetic vasoconstrictor mechanisms with resultant pooling of blood in peripheral veins, especially in the standing position. The orthostatic hypotension and reduction in pulse pressure accompanying the use of guanethidine support the view that pooling of blood in leg veins with decrease in venous return and hence in cardiac output is responsible for the reduction in blood pressure. There is no direct evidence from the available data, however, that eliminates the alternate hypothesis that guanethidine primarily affects myocardial contractility rather than venous return.

As shown in table 1, reduction in cardiac output in association with use of guanethidine was accompanied by decrease in heart rate such that the volume of blood pumped per

beat of the heart remained relatively constant. This observation suggests that guanethidine inhibits sympathetic cardio-accelerator stimuli. The absence of changes in stroke volume argues against a primary effect of guanethidine on myocardial contractile force.

#### Renal Circulation

Inulin clearance ( $C_{In}$ ) was used to estimate glomerular filtration rate (GFR), and clearance of para-aminohippurate ( $C_{PAH}$ ) to estimate renal plasma flow (RPF) in 11 hypertensive patients. In 7 of these, observations were made in the supine and 40° head-up tilted positions both before and during guanethidine administration. In all subjects, control measurements, made while the patient received no hypotensive drugs, were compared with measurements made during the height of the hypotensive effect of guanethidine, about 1 to 2 weeks following or preceding the control determinations.

Table 2 presents average changes in renal circulation and figure 4 the individual variations in renal vascular resistance. Prior to treatment, glomerular filtration rate in these hypertensive patients averaged about 70 per cent of normal, and renal plasma flow was even lower, the average of the group being 45 per cent of normal. Before guanethidine, head-

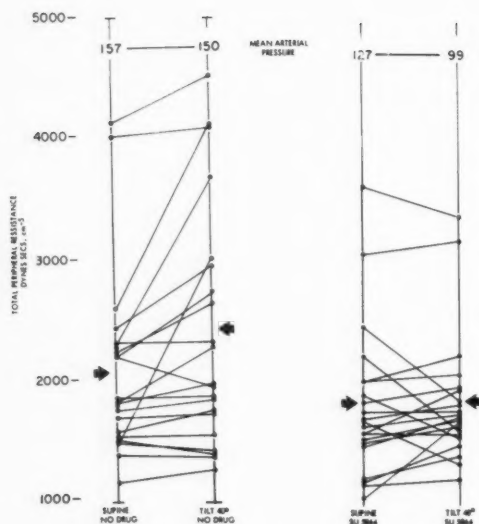


Figure 3

Changes in calculated total peripheral resistance accompanying guanethidine administration. Arrows point to the mean of each vertical column.

up tilt to 40° reduced  $C_{in}$  and  $C_{PAH}$  by about 30 per cent, despite lack of significant change in blood pressure. Administration of guanethidine was accompanied by reduction in GFR and RPF in both lying and "standing" positions in 7 individuals. These measurements were unchanged in 3 and rose slightly in 1. Blood pressure decreased proportionately more than did renal plasma flow, so that calculated renal vascular resistance diminished slightly as compared to pretreatment values in either position. This slight decrease in renal vascular resistance was minor in comparison with the reduction in the absolute values for glomerular filtration rate and renal plasma flow accompanying administration of the drug. During guanethidine treatment, GFR averaged one third and RPF one fourth of the pretreatment values in the "standing" (40° tilted) position. Filtration fraction, the ratio of GFR to RPF, decreased under the influence of guanethidine, indicating proportionately greater fall in filtration than in blood flow. This observation suggests that the reduction in arterial pressure is primarily re-

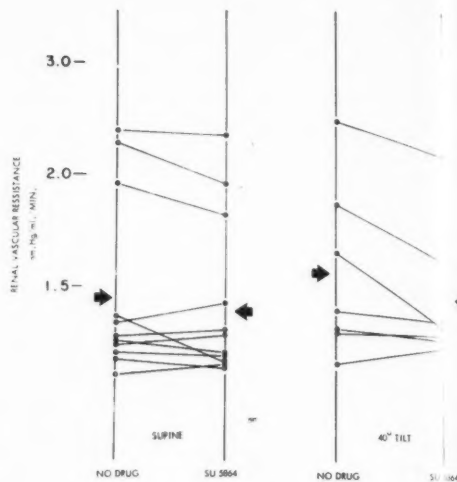


Figure 4

Changes in renal vascular resistance accompanying guanethidine administration.

sponsible for the observed changes in GFR and RPF.

Guanethidine treatment impairs renal function, presumably because the minimal reduction in vascular resistance that accompanies its use is inadequate to permit maintenance of blood flow and filtration in the face of the marked reduction in blood pressure. Similar changes have been observed acutely during parenteral administration of ganglionic blocking agents by Ford,<sup>10</sup> who suggests, apparently from detailed experience with one patient, that initial impairment of renal function returns to pretreatment levels within 10 days of treatment with hexamethonium despite continuing reduction in blood pressure. This return of renal function to pretreatment values during continued reduction in pressure did not occur in our patients, 5 of whom had been receiving guanethidine 20 or more days before renal function was measured.

It is not surprising in view of these marked reductions in renal function to find that determinations of blood urea nitrogen rose during treatment with guanethidine in about half of the patients studied, but only if the blood urea nitrogen exceeded 25 mg. per cent in the control period. Elevation of blood urea

**Table 2**  
*Effects of Guanethidine on Renal Circulation*

		Lying, no drug	Lying, guanethidine	40° tilt, no drug	40° tilt, guanethidine
$C_{IN}$	ml./min.	70 ± 43	58 ± 35	44 ± 28	32 ± 21*
$C_{PAH}$	ml./min.	258 ± 158	231 ± 125	185 ± 121	150 ± 71*
Mean arterial pressure	mm. Hg	157 ± 24	127 ± 16	151 ± 24	109 ± 22*
Renal vascular resistance	mm. Hg ml./min.	.86 ± .72	.81 ± .69	1.15 ± .76	.94 ± .61
Filtration fraction		.28 ± .09	.25 ± .05	.31 ± .19	.21 ± .09

Figures are mean ±1 standard deviation;  $C_{IN}$ , clearance of inulin;  $C_{PAH}$ , clearance of para-aminohippurate

\*Significantly different from values supine without drug ( $p < .05$ ).

nitrogen during guanethidine administration was of moderate magnitude, the largest change being from 46 to 78 mg. per cent. In no case was cessation of drug therapy required because of oliguria or progressive azotemia. As judged by the blood urea nitrogen, renal function returned to pretreatment levels soon after the drug was stopped.

#### Summary

Guanethidine, a new synthetic hypotensive drug that probably interferes with release of norepinephrine from sympathetic nerve endings and that does not inhibit parasympathetic activity, has proved an effective agent in reducing blood pressure in 25 hypertensive patients studied for periods up to 6 months. Untoward effects have been limited to orthostatic hypotension and mild diarrhea.

The drug apparently lowers blood pressure by reduction in cardiac output rather than by relaxation of the arterioles. Reduction in renal blood flow and glomerular filtration rate accompanied administration of the drug, but in no case did progressive azotemia or oliguria occur.

This agent is an extremely potent hypotensive drug with a remarkably prolonged duration of action and with none of the parasympatholytic side effects produced by ganglionic blocking agents.

#### Acknowledgment

Grateful appreciation is expressed to Mrs. M. P. Stephenson, Mrs. Virginia Stewart, Mrs. Betty Cauthorn, and Misses Mary Andre and Carol Aleock for expert technical assistance.

#### Summario in Interlingua

Guanethidina—un nove droga hypotensive synthetic que probabilemente inhibi le liberation de norepinephrina per le terminos sympathico-nervose e que demonstratemente non inhibi le activitate parasympathic—se ha provate capace a efficacemente reducer le tension del sanguine in 25 patientes hypertensive qui esseva studiate durante periodos de usque a 6 menses. Le adverse effectos lateral esseva restringite a hypotension orthostatic e leve grados de diarrhea.

Apparentemente le droga reduce le tension del sanguine per reducer le rendimento cardiac plus tosto que per relaxar le arteriolas. Le administration del droga esseva accompagnate de reductiones in le fluxo de sanguine renal e in le intensitate del filtration glomerular, sed azotemia progressive o oliguria non occurreva in ulle del casos.

Iste agente es un potentissime droga hypotensive. Le duration de su effecto es remarcabilemente long. Illo es characterisate per nulle del effectos lateral parasympatholytic que es producite per le agentes de blocage ganglionie.

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## Medical Eponyms

By ROBERT W. BUCK, M.D.

**Schonlein's Purpura.** In 1837 there was published at Würzburg a work entitled *Allgemeine und specielle Pathologie und Therapie*. This consisted of students' transcripts of lectures delivered by Johann Lucas Schonlein (1793-1864), Professor of Internal Medicine at Zürich. The following description of *peliosis rheumatica* is taken from the third edition, volume 2, pp. 48-49, Würzburg, 1837.

"The spots are never confluent as they often are in Wehrholf's (sic) Disease. . . .

"The patients have either previously suffered with rheumatism, or rheumatic symptoms appear coincidentally.

"The characteristic spots of the disease appear first on the extremities in the majority of cases, especially the lower, rarely the upper ones, and here only up as far as the knee. The spots are small, the size of a lentil or a millet seed, bright red, not raised above the skin, and disappear on pressure by the finger. They gradually become dirty brown or yellow, and the skin over them undergoes a somewhat branny desquamation. The eruption follows a sporadic course, often over a period of several weeks. . . .

"This disease has been confused with the *morbus maculosus Werlhofii*. The absence of the so-called purpuric phenomena in the mouth . . . the lack of all hemorrhage, the peculiarity of the eruption . . . the joint involvement (which does not occur in that disease), and the absence of nervous phenomena, such as marked prostration and weakness, further assure the diagnosis."

# Selective Inhibition of the Sympathetic Nervous System in Man with Bretylium Tosylate, a New Antihypertensive Agent

By EDWARD D. FREIS, M.D., TAKERO SUGIURA, M.D., AND DOROTHY LIPTAK, M.D.

**B**OURA and his associates have demonstrated that bretylium tosylate (Darenthin)\* produces a selective block of the sympathetic nervous system.<sup>1</sup> This benzyl quaternary ammonium compound appears to accumulate preferentially in peripheral sympathetic neurones. Unlike adrenergic blocking agents the effects of released or injected epinephrine and norepinephrine are not antagonized, and unlike ganglion-blocking drugs the parasympathetic nervous system is not inhibited at therapeutic dose levels of bretylium.<sup>1</sup> Clinical trials in hypertensive patients indicate that orally administered bretylium tosylate causes a predominantly orthostatic fall of blood pressure comparable to that achieved with the ganglion-blocking drugs but without the side effects of parasympathetic blockade.<sup>1,2</sup> The following report summarizes our experience to date with this new agent.

## Inhibition of Sympathetic Vasoconstrictor Reflexes

The reflex activity of the sympathetic vasoconstrictor system was assessed in normotensive men as follows: 1. The Valsalva "overshoot" of arterial pressure was recorded directly with a strain gage from a needle placed in the brachial artery. After a deep inspiration the subject blew forcefully and steadily into a closed tube for 10 seconds to produce a sustained increase in intrathoracic pressure. The expiratory effort was then suddenly and completely released. The resulting "overshoot" of arterial pressure has been

shown to be due to a reflex sympathetic discharge occurring during the period of diminished cardiac return and, hence, cardiac output.<sup>3</sup> 2. The cold pressor response was recorded by placing the patient's hand in a mixture of water and ice for 1 minute. 3. Reflex sympathetic vasoconstriction in the digit was recorded from a plastic cup sealed to a finger and attached through a short length of plastic tubing to a sensitive strain gage (digital plethysmograph). The decrease in pulse and finger volume indicating vasoconstriction was recorded following the stimulus of a deep breath. The latter has been shown to initiate a reflex sympathetic discharge to the digit. Following the control determinations of the sympathetic reflex responses, which were carried out with the subjects resting supine in a warm room, bretylium tosylate diluted in isotonic saline to a final concentration of 15 mg. per ml. was injected slowly intravenously over a period of 4 minutes. No subjective side effects were complained of during or following the injection. Dosages of 50, 100, and 150 mg. were given in different subjects.

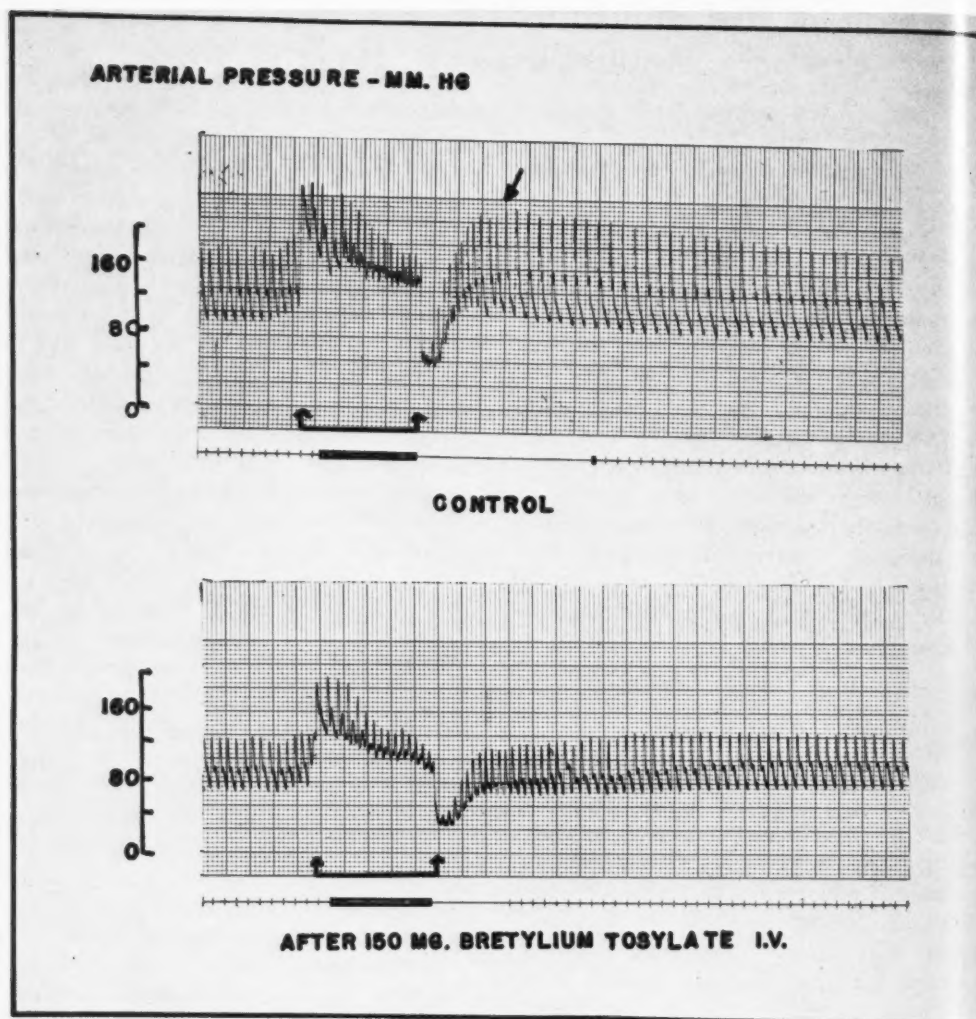
Partial inhibition of the sympathetic vasoconstrictor reflexes appeared at a dose level of 50 mg. (approximately 0.7 mg. per Kg.) of bretylium tosylate intravenously. Complete inhibition of the Valsalva "overshoot" (fig. 1) and of the digital vasoconstrictor response to a deep breath (fig. 2) was accomplished at a dose level of 150 mg. (approximately 2 mg. per Kg.). This is comparable to a dose of 50 mg. of hexamethonium chloride intravenously, which produces a similar blockade of these reflex responses.<sup>4</sup>

The cold pressor response was inhibited but not completely blocked by bretylium tosylate even in doses of 150 mg. (fig. 3). By contrast, hexamethonium 50 mg. intravenously, usually

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**Figure 1**

*Recordings of arterial pressure illustrating abolition of the vasopressor "overshoot" following the Valsalva maneuver in a 38-year-old Negro man with essential hypertension. During interval between arrows on the baseline the patient blew forcibly into a closed tube. In the control period (upper tracing) following release of the expiratory effort note hypertensive "overshoot," indicated by the upper arrow. After 150 mg. of bretylium tosylate intravenously (lower tracing) the overshoot was abolished.*

blocked this response completely.<sup>4</sup> The cold pressor test, however, is a complex response involving not only an immediate reflex vasoconstriction but also a delayed pressor effect, which may be due to adrenal discharge. In this connection Boura has reported that in

animals bretylium, unlike the ganglion-blocking drugs, does not block the adrenal discharge of catecholamines following sympathetic stimulation. It is possible that the failure to block the delayed response of the cold pressor test in man is due to this phenomenon.

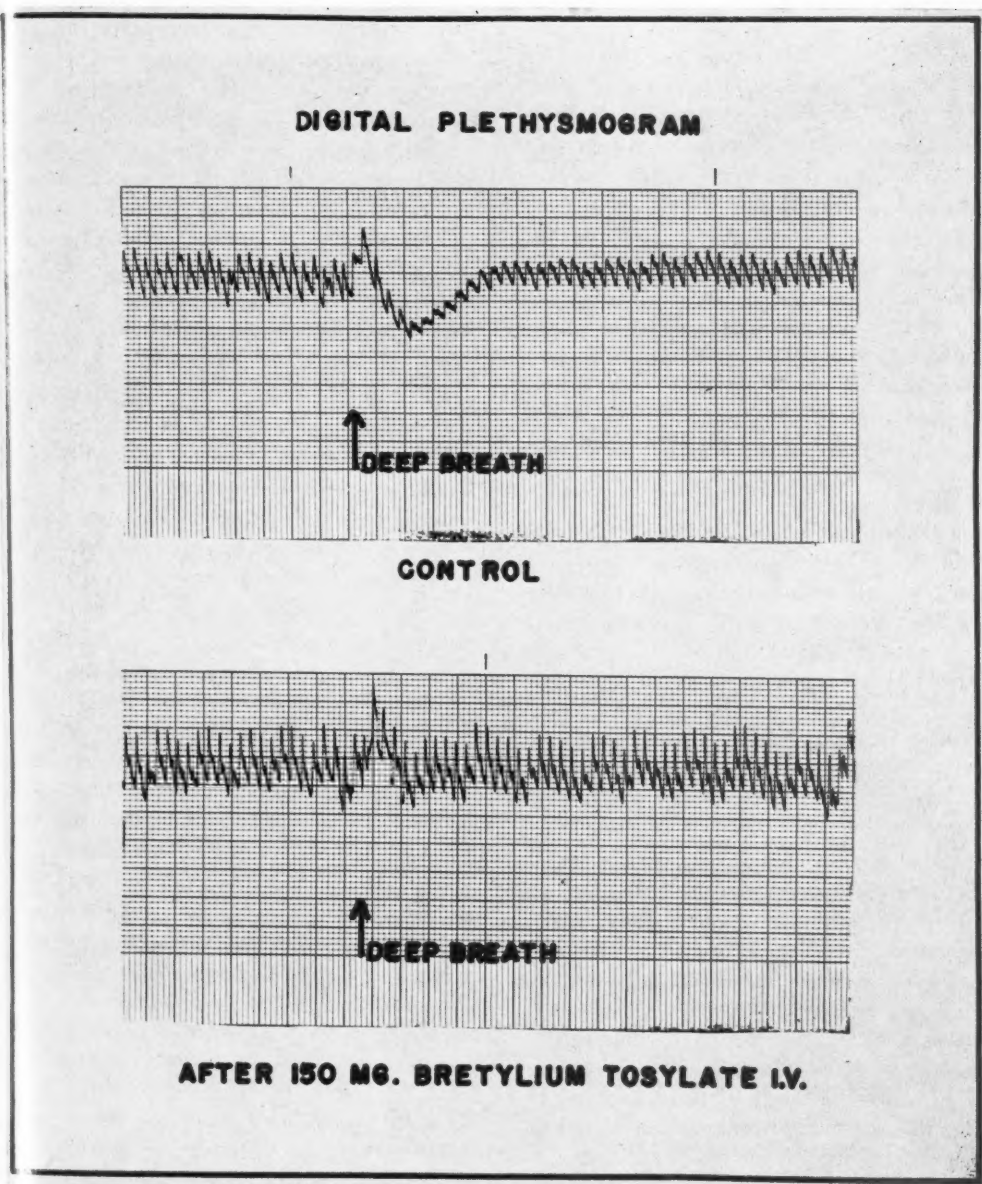


Figure 2

Recordings of digital plethysmograms in a 41-year-old man with essential hypertension. In the control period (upper tracing) following a deep breath a vasoconstrictor response occurred in the digit as indicated by diminution of both pulse and digit volume. Following 150 mg. of bretylium tosylate intravenously this reflex vasoconstrictor response was abolished (lower tracing).

Orthostatic hypotension was minimal at the 50-mg. dose, but moderate to severe at the 100-mg. level. This result is similar to our previous experience with hexamethonium, that only partial inhibition of sympathetic vasoconstrictor reflexes is required to produce significant orthostatic hypotension.

#### **Dose-Response Relationships**

Effective intravenous doses were defined as the amount required to produce a significant orthostatic hypotension. In 4 hospitalized hypertensive subjects tested this dose varied between 50 and 150 mg. Orthostatic hypotension appeared within 10 minutes after the intravenous dose. The supine blood pressure was only moderately affected by these dosages. There were no side effects except for slight postural faintness.

On subsequent days bretylium tosylate was administered orally in increasing dosages once daily in the morning until significant orthostatic hypotension occurred. This was done in an attempt to establish a relationship between parenteral and oral dosages. The ratio between effective oral and intravenous dosages varied between 8 to 1 and 24 to 1 in different patients. Since bretylium is a quaternary ammonium compound it was not surprising that absorption was poor after oral administration.

#### **Therapeutic Results in Hypertensive Patients**

Sixteen ambulatory patients with moderate to severe hypertension who had been under prior treatment with other agents were treated with bretylium tosylate for periods varying from 1 to 5 months. Bretylium was given alone in 8 patients. In the remainder it was substituted for a blocking agent without changing the adjunctive medication, which consisted of chlorothiazide or hydrochlorothiazide and in 2 patients of small doses of hydralazine. Administration of bretylium was begun at a dose of 200 mg. 3 times daily: after breakfast, at 2 p.m., and 10 p.m. (600 mg. daily). Modification of dosage was then made upward or downward, depending on the response of the blood pressure. In 11 patients blood pressure levels were recorded usually in the sitting and erect positions twice daily in the home.

Effective antihypertensive dosage varied widely in different patients. In the group without adjunctive therapy, 600 mg. of bretylium daily was the lowest effective dose and 3,000 mg. the highest. Several patients, however, failed to exhibit an antihypertensive effect on 3,000 mg. per day. Efforts to raise the dosage above this level were not attempted because of the large number of tablets required.

In the patients receiving adjunctive therapy (primarily chlorothiazide) 200 mg. of bretylium tosylate was the smallest effective daily dose, whereas one patient failed to exhibit significant orthostatic hypotension on 3,000 mg. daily. Although the series is too small for accurate appraisal of the average dose, the majority of the patients who responded exhibited moderate reduction of supine blood pressure and definite but tolerable orthostatic hypotension in a dosage range of 1,800 to 2,400 mg. without chlorothiazide and 1,000 and 1,200 mg. with chlorothiazide.

The only side effects encountered that could be attributed to bretylium tosylate were orthostatic faintness similar to that encountered with the ganglion-blocking drugs, and failure of ejaculation in a few male patients similar to that encountered after guanethidine.<sup>5</sup> Several patients complained of tenderness over the parotid glands with pain in these areas on mastication. Orthostatic hypotension with faintness and weakness tended to occur most commonly in the morning, and for this reason the morning dose was given after rather than before breakfast. As with the ganglioplegic agents careful dosage adjustment and periodic readjustment were required to obtain blood pressure control on the one hand and avoid postural faintness on the other. Parasympathetic blocking effects such as constipation, dryness of the mouth, difficult micturition, and failure of visual accommodation were entirely absent. Diarrhea, which may occur after guanethidine,<sup>5, 6, 8</sup> was not noted by the patients taking bretylium. The heart rate did not change significantly, and there were no arrhythmias. Evidences of "tolerance" were simi-

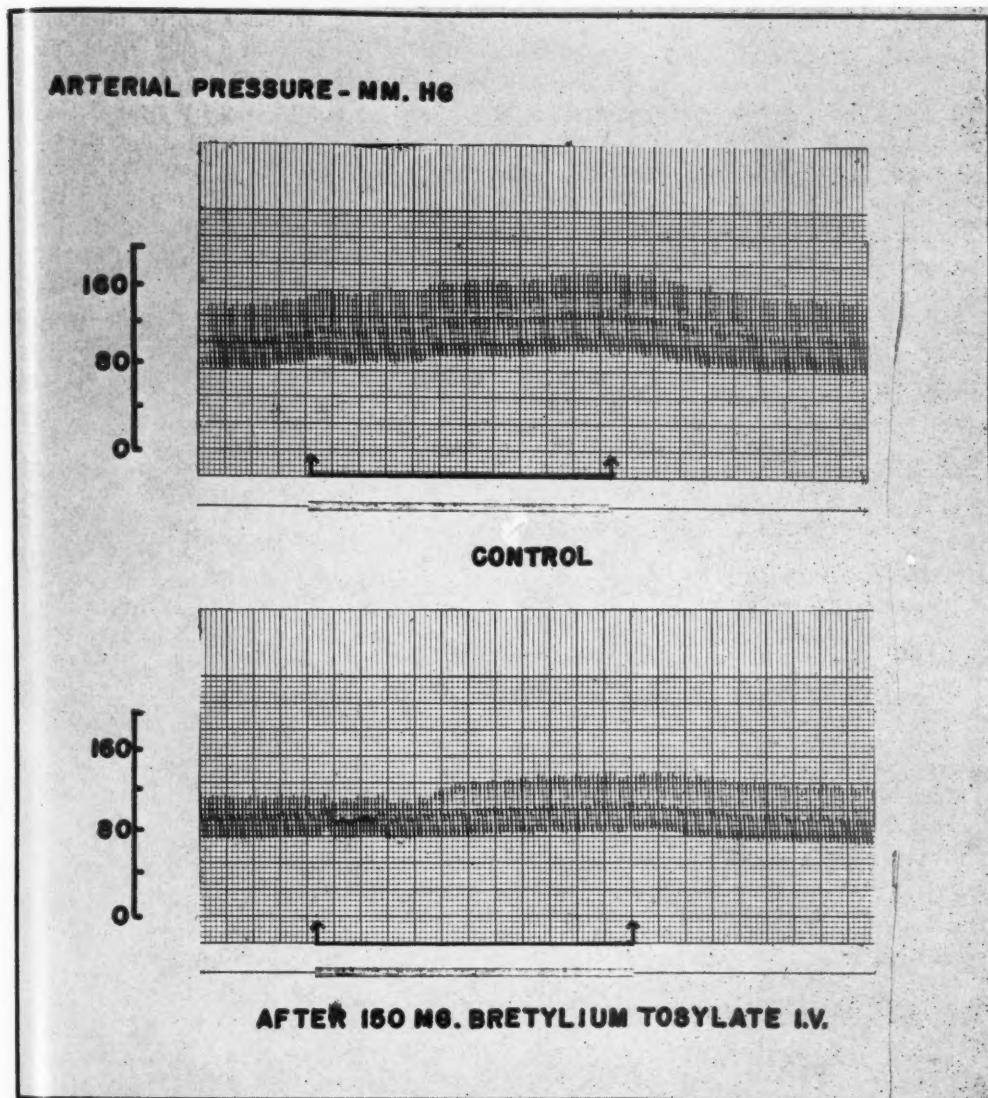


Figure 3

Recordings of arterial pressure during the "cold pressor" response in a 32-year-old normal man. The subject's hand was immersed in ice water during the 1-minute period indicated by the baseline arrows. As compared to control response (upper tracing) onset of pressor effect was delayed after 150 mg. of bretylium tosylate intravenously (lower tracing) but not completely blocked.

lar to those encountered with the ganglion-blocking drugs. For example, some patients were responsive initially to smaller dosages than were required for long-term control of

the blood pressure. Also, with continued treatment there tended to be a narrowing of the early, wide spread between the blood pressure in the supine and erect positions.

### Discussion

In general, the present observations confirm those of the prior British investigators.<sup>1,2</sup> The principal advantage of bretylium tosylate is its lack of parasympathetic blocking action. However, it shares with the ganglion-blocking agents the ability to produce orthostatic faintness and collapse, plus a wide dose-response range in different patients. In order to achieve optimal results these characteristics necessitate painstaking and individualized dosage adjustments similar to those required with the ganglioplegic drugs. This difficulty suggests that bretylium tosylate will be used more advantageously in patients with severe disease whose hypertension cannot be controlled satisfactorily with chlorothiazide, either alone or with small dosages of hydralazine or reserpine. In these patients the ability of bretylium to produce an inhibition of sympathetic vasoconstriction comparable to that achieved with the ganglioplegic agents but without their parasympathetic blocking effects is a definite advantage. Present results suggest, however, that more potent drugs (guanethidine or ganglion-blocking agents) must be substituted in those patients who remain unresponsive to bretylium tosylate in dosages within a practical, clinically acceptable range.

Bretylium tosylate differs somewhat from guanethidine, which also produces a selective blockade of the peripheral sympathetic system.<sup>5-8</sup> The latter agent produces bradycardia and diarrhea, both of which can be blocked with atropine or similar agents suggesting parasympathetic predominance. Another disadvantage of guanethidine is its prolonged duration of action. At a given dose level the maximum antihypertensive effect may not occur until 4 or 5 days; and after a hypotensive episode, disabling orthostatic effects may persist for several days. This cumulative action of guanethidine requires that elevations of dosage must be accomplished at weekly rather than daily intervals if hypotensive reactions are to be avoided.

Since bretylium has a shorter duration of action averaging about 8 hours, rapid dosage adjustment is permissible and the effects of an overdose are not unduly prolonged. On the other hand, the high dosage requirement is a disadvantage of bretylium tosylate that is aggravated by the failure to produce a tablet containing more than 200 mg. of the drug. Ingestion of more than 3 tablets 3 times daily is psychologically disturbing to most patients. Concomitant administration of chlorothiazide usually permits reduction in the dosage requirement of bretylium to a tolerable range, but this was not true in all cases. In addition to chlorothiazide Smirk and Hodge<sup>2</sup> have added one of the more potent ganglioplegic drugs in such instances, thus providing an effective but somewhat complicated regimen. It is hoped that further developments will result in a peripheral sympathetic blocking drug that combines the tablet potency of guanethidine with the lack of either parasympathetic blocking or enhancing effects of bretylium.

### Summary and Conclusions

Bretylium tosylate inhibited sympathetic vasoconstrictor reflexes in man, but unlike the ganglioplegic drugs it produced no parasympathetic blocking side effects. As with other quaternary ammonium salts the drug was poorly absorbed from the gastrointestinal tract.

Administered orally to hypertensive patients, bretylium tosylate produced a reduction of blood pressure that was primarily orthostatic. Dosage requirements in general were large and in some instances were so excessive as to be therapeutically impractical. Effective dose levels could be reduced somewhat by the addition of chlorothiazide. The only side effects or toxic reactions encountered were postural faintness and syncope (the avoidance of which required scrupulous care in dosage adjustment), pain and tenderness over the parotid glands, and failure of ejaculation in a few patients.

### Summario in Interlingua

Tosylato de bretylium inhibiva sympathic reflexos vasoconstrictori in humanos, sed—per contrasto con le drogas ganglioplegie—illo produceva nulle effecto lateral de blocage parasymphic. Como es etiam le caso in altere sales quaternari de ammonium, le droga esseva mal absorbite ab le vias gastrointestinal.

Administrare per via oral a patientes hypertensive, tosylato de bretylium produceva un reduction del tension sanguinee que esseva primarimente orthostatice. Le requirimentos del dosage esseva generalmente grande. In certe casos illos esseva si excessive que le therapia deveniva impracticabile. Le nivellos del dosage efficace poteva esser reduce in un certe mesura per le addition de chlorothiazida. Le sol adverse effectos lateral o reacciones toxic esseva debilitate postural e syncope. Pro evitar iste ultime, le plus scrupulose attention debeva esser prestate al adjustment del dosage. In plure patientes dysfunction del ejaculation esseva notate.

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### On Cardiac Murmurs

By AUSTIN FLINT, M.D.

Case 2. In February, 1861, I was requested to determine the murmur in a case at the Charity Hospital, New Orleans. I found an aortic direct and an aortic regurgitant murmur, both murmurs being well marked. There was also a distinct pre-systolic murmur within the apex, having the blubbery character. On examination after death, the aorta was dilated and roughened with atheroma and calcareous deposit. The aortic segments were contracted, and evidently insufficient. The mitral curtains presented no lesions; the mitral orifice was neither contracted nor dilated, and the valve was evidently sufficient. The heart was considerably enlarged, weighing 17½ oz., and the walls of the left ventricle were an inch in thickness.—*Am. J. M. Sc. n.s.* 44: 29, 1862.

# Tricuspid Stenosis with Pulmonary Atresia

## A Cineangiographic-Pathologic Correlation

By MILTON H. PAUL, M.D., AND MAURICE LEV, M.D.

**T**RICUSPID stenosis associated with pulmonary atresia or stenosis is a relatively uncommon complex that has been recognized pathologically for many years.<sup>1</sup> More recently the clinical findings have been documented and summarized.<sup>2</sup>

The course of the circulation in tricuspid stenosis with pulmonary atresia is essentially similar to that in tricuspid atresia with the right atrial blood being shunted into the left cardiac chambers through a patent foramen ovale. The hemodynamic role of the obstructed, blind right ventricular chamber remains, however, inadequately defined. This report deals with cineangiographic and physiologic observations in an infant with this complex and presents a correlative analysis of this material with the pathologic substratum.

### Clinical Examination

A 15-week-old female infant, cyanotic since birth, was admitted for study because of increasing cyanosis and respiratory distress.

Examination revealed generalized slight cyanosis. The liver was enlarged 4 cm. below the right costal margin and was pulsating. There was a prominent lower left sternal border systolic cardiac impulse. No thrills were palpated. The first heart sound was of normal intensity, and there was a loud early systolic click, maximum at the upper left sternal border. The second heart sound was single-sounding and of slightly increased intensity along the left sternal border. A harsh short grade-III systolic murmur was maximum at the mid-left sternal border.

The electrocardiogram (fig. 1) indicated right atrial hypertrophy and severe left ventricular pre-

ponderance. The x-ray showed the heart to be moderately enlarged, with an abnormally prominent right atrial segment, decreased pulmonary vasculature, and left aortic arch.

Cyanotic spells and episodes of severe respiratory distress recurred with increasing frequency in the hospital, and the infant died 5 days after catheterization at 16 weeks of age.

### Cardiac Catheterization and Cineangiocardiograms

Cardiac catheterization was performed under mild sedation (Demerol-Phenergan-sparine mixture) and the catheter was inserted via the right saphenous vein. From the right atrium it was possible to enter a ventricular chamber located in the right anterior portion of the cardiac silhouette. This chamber was entered repeatedly, but at no time could the catheter be manipulated to enter an outflow tract. No interatrial communication could be demonstrated by passage of the catheter into the left atrium. Blood samples for oxygen analysis and blood pressures were recorded (table 1 and fig. 2).

Cineangiocardiograms were made at 48 frames per second with the rapid (1 sec.) injection of 3 ml. of 90 per cent Hypaque, twice into the right ventricle and once into the right atrium (fig. 3). The right ventricular chamber remained opacified for an unusually long period, over 480 frames (10 sec.), from the instant of injection. Regurgitation from right ventricle to right atrium was clearly demonstrated throughout this period.

### Postmortem Examination of Heart

On gross examination the heart (figs. 4 and 5) weighed 39.5 Gm. (fixed) and was enlarged. The apex was formed by the left ventricle. From the base 2 arteries emerged. The larger was situated posteriorly and to the right; the smaller anteriorly and to the left. The mutual relationships of the various chambers were normal. The cardiac measurements are given in table 2.

The right atrium was markedly enlarged and thickened, being larger and thicker than the left atrium. The right atrium received the superior and inferior venae cavae and the coronary sinus in a normal manner. The limbus was well formed, and the foramen ovale was patent about 0.8 cm.

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Supported in part by a research grant (H-3351) from the National Heart Institute, U.S. Public Health Service.

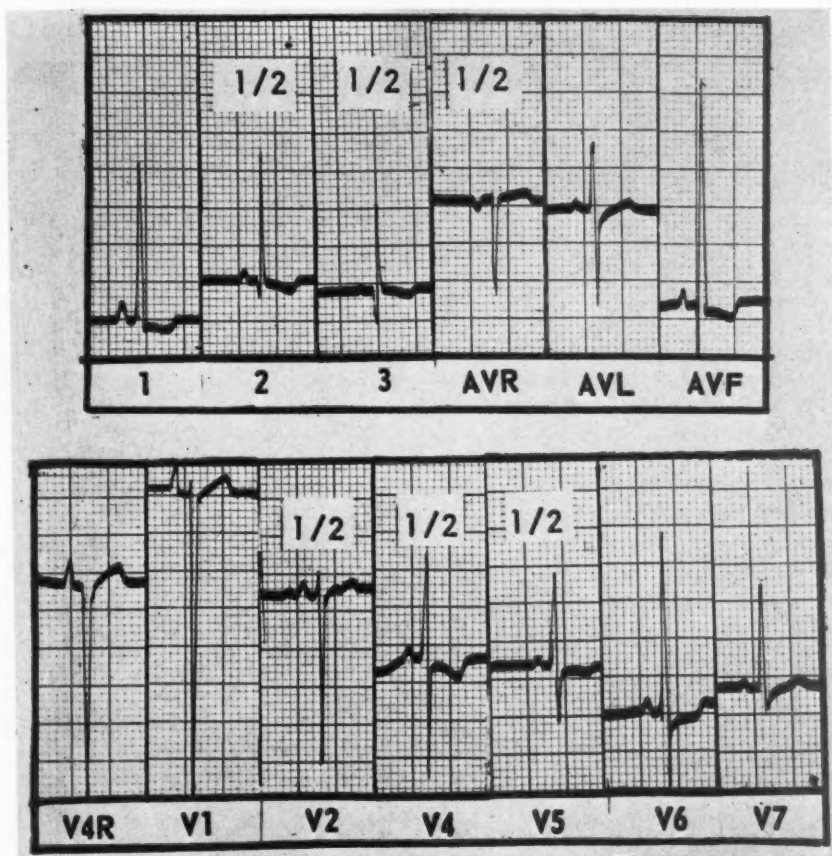


Figure 1

*Electrocardiogram showing marked left ventricular preponderance.*

The tricuspid orifice was very small and the tricuspid valve consisted of 3 attenuated cusps with very small papillary muscles.

The right ventricle was a minute chamber; but its wall was markedly thickened, its thickness being equal to that of the left ventricle. No artery emerged from this chamber.

The left atrium was normal in size or slightly larger than normal and it was distinctly smaller than the right atrium. Its wall was of normal thickness and definitely thinner than that of the right atrium. The mitral orifice was normal or slightly increased in size and the mitral valve was normally formed.

The left ventricular chamber was normal in size, but its wall was thicker than normal. The ventricular septum was intact. From this chamber emerged the aorta. The aortic orifice was normal

or slightly increased in size and the valve was bicuspid with a right anterior and a left posterior cusp. The coronary ostia were normal and the coronary arteries were normal in distribution. The ductus arteriosus was patent and led into the pulmonary trunk, which was distinctly smaller than the aorta. The wall of the pulmonary trunk was thinner than normal. The pulmonary trunk ended blindly at the base of the heart, but it gave off the 2 pulmonary arteries in a normal manner. The brachiocephalic arteries arose normally.

In the right atrium there was an accentuation of the normal endocardial thickening over the limbus, the entry of the inferior vena cava, the posterior crest, and the endocardium proximal to the tricuspid annulus. In the right ventricle the endocardium was diffusely thickened and whitened, and a gross diagnosis of fibroelastosis could be

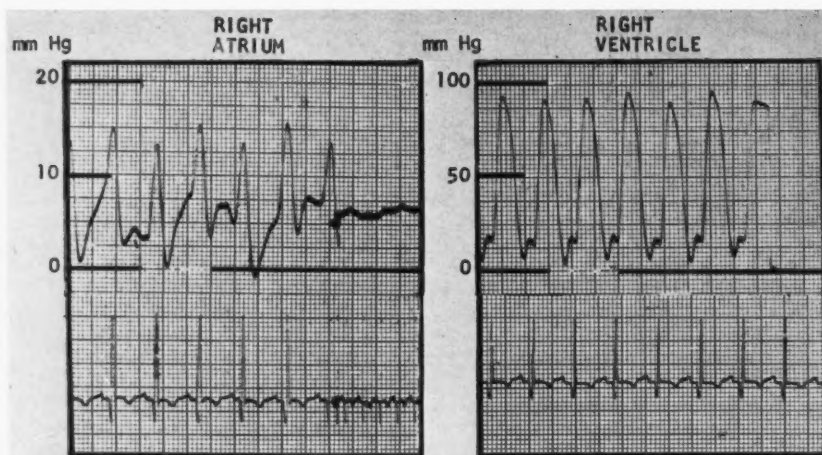


Figure 2

*Pressure tracings from right atrium and right ventricle.*

Table 1

*Catheterization Data*

Catheter site	Oxygen saturation, %	Oxygen content, vol. %	Pressure, mm. Hg
Superior vena cava	6.5	1.6	
Right atrium	4.1	1.0	"a" wave 14 (mean 7)
Right ventricle (a)	7.6	1.8	75/10
Right ventricle (b)	8.1	1.9	90/15
Femoral artery	21.8	5.2	90/65

made. No abnormal changes could be detected in the left atrial and ventricular endocardium.

The tricuspid leaflets were diffusely thickened, the thickening involving the edge, substance, and base. They were connected by abnormally short chordae to short papillary muscles. There was marked thickening of the line of closure of the mitral valve that was almost nodular in nature, involving the complete anterior leaflet and to a less extent the inferior leaflet. In place of a pulmonic valvular structure there were several fused folds of endocardial tissue. All the aortic cusps, especially the right anterior, were thicker than normal.

#### Discussion

An opportunity was presented during cardiac catheterization to study the hemodynamic function of the obstructed right ventricular chamber in a heart with tricuspid stenosis, pulmonary atresia, and an intact ventricular septum.

The pathologic anatomy of the present case falls into the usual pattern of this complex. The tricuspid orifice in most cases is small due to a small annular opening rather than to a stenosis of the valve structure itself. The valve usually consists of thickened leaflet tissue connected by short chordae to small papillary muscles. The pulmonic orifice is small or completely absent. When small, the annular opening is reduced in size with a typical ring type of pulmonary valvular stenosis.

When the orifice is obliterated, agglutinated valvular cusps may be recognized or no distinct valve may be recognized. As in all cases of tricuspid stenosis and atresia, there is an atrial septal defect (patent foramen ovale), hypertrophy of the right atrium and left ventricle, and a diminutive right ventricular chamber. There is, in most cases, a markedly

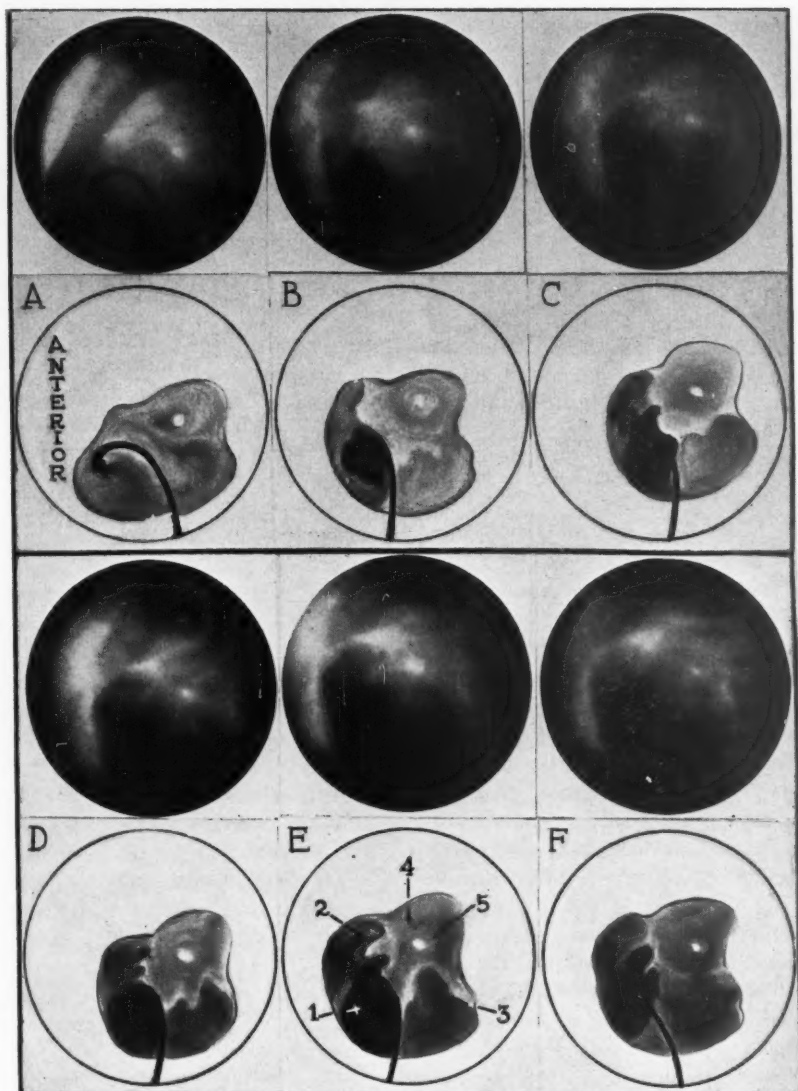


Figure 3

Cineangiocardigrams (lateral) following injection of 3 ml. of Hypaque (90 per cent) into right ventricle: A. Onset of injection into right ventricle (1). B and C. Complete opacification of right ventricle (1) and regurgitation into right atrium and atrial appendage (2). D and E. Opacification of left atrium and left ventricle (3). F. Opacification of aorta (4) filling from left ventricle, and pulmonary artery (5) filling via patent ductus arteriosus. Note that the right ventricle (1) remains heavily opacified in F, approximately 8 seconds after completion of dye injection.

thickened right ventricular wall with diffuse fibroelastosis of the endocardium. Increased focal endocardial hypertrophy is noted in the

right atrium in most cases, and there are hemodynamic changes in the mitral and aortic valves. The ventricular septum is usually



**Figure 4**

*External anterior view of the open fixed heart: Pu, pulmonary artery; A, aorta; RA, right atrium; RV, right ventricle, and LV, left ventricle.*



**Figure 5**

*Internal view of the right atrium and inflow tract of the right ventricle: L, limbus fossa ovalis; E, Eustachian valve; C, coronary sinus; TV, tricuspid valve, and W, parietal wall of the right ventricle.*

intact. A patent ductus arteriosus of moderate or small caliber is usually present and it represents the primary route of blood to the pulmonary circuit.

These anatomic findings take on physiologic meaning when correlated with the catheterization and cineangiocardigraphic findings. The injection of 3 ml. of contrast material into the obstructed ventricular chamber, of approximately 2 to 3 ml. volume, probably replaced a large proportion of the ventricular blood and then provided a continuous but diminishing opacification of the chamber for about 10 seconds or 25 cardiac contractions. The cineangiocardigram demonstrated that the anatomically stenotic tricuspid orifice was also a regurgitant orifice. These observations are necessarily made with the cardiac catheter traversing the tricuspid valve and the role of the catheter in inducing or augmenting the regurgitation is undefined. It seems quite likely, however, that there is usually a bidirectional movement of blood across the tricuspid orifice in this condition. It can be postulated that the bidirectional movement of blood associated with the tricuspid regurgitation prevents the diminutive ventricle with obstructed outflow from becoming obliterated by stasis and thrombosis. This latter finding has been described in tricuspid stenosis with pulmonary atresia.<sup>4</sup>

The right atrial pressure tracings show very prominent atrial systole "A" waves that are clearly reflected in the presystolic phase of the ventricular tracings with equal pressures. The atrial pressures recorded in early ventricular diastole are not much greater than comparable early diastolic pressures in the right ventricle and do not reflect a hemodynamically significant tricuspid stenosis. It seems likely, however, that the usual transvalvular pressure gradient tracings seen in isolated tricuspid valvular stenosis might not be obtained in this complex because of the extremely small volumes of blood flowing across the stenotic and regurgitant tricuspid orifice. The pressure curves recorded from the right ventricle varied from 75/12 to 90/15 mm. Hg during the catheterization, and the triangular ejection curve is not unlike that observed in the obstructed chamber of severe pulmonary valvular stenosis.

In this complex the tricuspid valve is patent and blood enters the right ventricle. Because of the obstruction at the outlet and the stenosis at the inlet, however, considerable right ventricular hypertension is present. The right ventricular wall is correspondingly thickened. The elevated right ventricular pressure may lead to the development of tricuspid regurgitation. The right ventricular volume is small, probably because of the small

Table 2

## Heart Measurements (Fixed Heart)

Wall thickness	Cm.
Right ventricle	
Pulmonic area	0.7
Tricuspid area	0.9
Apical area	0.5
Left ventricle	
Maximum	0.9
Apex	0.4
Circumference of orifices	
Tricuspid	2.1
Mitral	3.6
Aortic	3.0
Internal wall measurements	
Right ventricle	
Inlet length	3.2
Inlet perimeter	1.6
Outlet length	3.2
Outlet perimeter	0.6
Left ventricle	
Inlet length	2.4
Outlet length	3.3
Perimeter	4.1

volume of blood entering and leaving this chamber. The fibroelastosis in the right ventricle may be the result of stasis, increased endomyocardial tension, or some other undefined factor.<sup>5</sup>

The right atrium is large and thick-walled due to the large volume and high pressure present in this chamber as a result of the tricuspid stenosis and the relative functional stenosis of the patent foramen ovale.

## Summary

An opportunity was presented during cardiac catheterization to study the hemodynamic function of the obstructed right ventricular chamber in a heart with tricuspid stenosis, pulmonary atresia, and an intact ventricular septum.

Cineangiocardigrams demonstrated that the anatomically stenotic tricuspid orifice was also a regurgitant orifice and it is postulated that the bidirectional flow of blood associated with the tricuspid regurgitation prevents the obstructed ventricle from becoming obliterated by stasis-thrombosis.

## Summario in Interlingua

Se presentava le opportunitate, durante catheterisation cardiac, de studiar le function hemodynamic del obstruite camera dextero-ventricular in un corde con stenose tricuspidie, atresia pulmonar, e un intacte septo ventricular.

Cineangiocardigrammas demonstrava que le anatomicamente stenotic orificio tricuspidie esseva etiam un orificio regurgitante, e il es postulate que le fluxo bidirectional de sanguine associate con le regurgitation tricuspidie preveni que le obstruite ventriculo es oblitterate per stase e thrombose.

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# Effects of Acute Hypoxia and Exercise on the Pulmonary Circulation

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**T**WO MAJOR obstacles complicate the study of the pulmonary circulation in man: the inaccessibility of the pulmonary vessels for direct cannulation, and the multiplicity of extravascular factors that influence pressure-flow-volume relationships within the lungs. New techniques have largely circumvented the first difficulty; the second difficulty is minimal in the normal resting subject, but is exaggerated by either physiologic stress, e.g., exercise, or by abnormalities of the heart or lungs.

Observations on a variety of experimental preparations have afforded considerable insight into the regulation of the pulmonary circulation. Particularly rewarding have been the demonstrations by Beyne in the dog<sup>1</sup> and by von Euler and Liljestrand in the cat,<sup>2-4</sup> that acute hypoxia, hypercapnia, or both elicit pulmonary hypertension. These observations constitute a landmark in studies of the regulation of the pulmonary circulation since they afforded an experimental tool for the production of a pulmonary pressor response, and provided a hypothesis,<sup>2-4</sup> which could be tested, concerning the adaptation of pulmonary capillary perfusion to alveolar ventilation. Others have subsequently reproduced the pressor response to acute hypoxia in animals<sup>5</sup> and in man;<sup>6</sup> attempts to reproduce the pulmonary pressor response to acute hypercapnia have yielded far less consistent results.<sup>7</sup>

The present studies were designed to eluci-

date some of the mechanisms involved in the pulmonary vascular responses of man to acute hypoxia and to acute hypercapnia. This first report compares the effects of acute hypoxia and of exercise on pressure-flow relationships in normal subjects, in patients with restricted vascular beds, and in a patient with sympathetic denervation of the lungs. The second paper, because of the special techniques involved, is confined to the effects of acute hypoxia on the pulmonary blood volume. The third considers the effects of acute hypercapnia on pressure-flow relationships in the pulmonary circulation.

## Methods

All patients underwent a preliminary period of adjustment to the laboratory, its personnel, and facsimiles of the experimental protocol; this consisted of trial runs on a variety of hypoxic breathing mixtures coupled with collections of arterial blood and expired gas. Those who tolerated these procedures well subsequently served as experimental subjects.

All tests were performed in the postabsorptive state, without medication. Venous catheterization of the right heart was performed in the usual manner<sup>8</sup> and the tip of the catheter was placed in the pulmonary artery. The combination of the right heart catheterization, arterial cannulation, and the open-circuit method for collection of expired gas supplied the samples necessary for the calculation of the oxygen uptake ( $\dot{V}O_2$ ), the respiratory exchange ratio ( $R_E$ ), and the cardiac output ( $\dot{Q}$ ) by application of the Fick principle. For the recording of pulmonary and systemic arterial pressures, Statham gages were used as pressure transducers, in conjunction with high-sensitivity carrier amplifiers and photographic registration of the cathode-ray images.

The protocols were designed to satisfy criteria for the "steady state."<sup>9</sup> In brief, these criteria consist of clinical evidence for stability of the respiration and circulation at each level of oxygenation, supplemented by the objective evidence (in the form of  $R_E$ ,  $\dot{V}O_2$ ) for the equality of gas exchange measured at the mouth to that occurring

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Table 1

*Changes in Ventilation and Gas Exchange during Acute Hypoxia in Ten Normal Subjects*

Subject	Age (yrs.)	Sex	BSA M. <sup>2</sup>	Breathing mixture: Ambient air			Breathing mixture: 12-14% O <sub>2</sub> in N <sub>2</sub>		
				$\dot{V}_E$ L./min./M. <sup>2</sup>	$\dot{V}_{O_2}$ ml./min./M. <sup>2</sup>	R <sub>E</sub>	$\dot{V}_E$ L./min./M. <sup>2</sup>	$\dot{V}_{O_2}$ ml./min./M. <sup>2</sup>	R <sub>E</sub>
O.S.	35	M	1.77	4.27	138	.85	5.26	147	.90
A.P.	48	M	1.78	5.08	129	.91	6.25	132	.98
W.M.	49	M	1.76	5.73	136	.92	7.04	147	.94
H.P.	44	F	1.56	4.61	125	.81	5.64	129	.90
H.M.	35	M	2.10	3.38	118	.88	4.12	127	.98
G.H.	35	F	1.54	4.25	140	.84	5.96	147	.94
E.J.	68	M	1.58	4.51	131	.86	5.03	132	.91
C.D.	51	M	1.71	4.20	104	.85	4.69	108	.91
B.J.	25	M	1.88	4.18	147	.84	4.61	148	.93
F.D.	48	M	1.80	4.96	124	.94	6.51	149	1.04
Average				4.52	129	.87	5.51	137	.92

 $\dot{V}_E$ , minute ventilation;  $\dot{V}_{O_2}$ , oxygen uptake; R<sub>E</sub>, respiratory exchange ratio.

Table 2

*Changes in Arterial Blood Oxyhemoglobin Saturation, Cardiac Output, Pulmonary and Systemic Artery Blood Pressures during Acute Hypoxia in Ten Normal Subjects*

Subject	Breathing mixture: Ambient air					Breathing mixture: 12-14 O <sub>2</sub> % in N <sub>2</sub>				
	Arterial blood O <sub>2</sub> sat. %	Cardiac output L./min./M. <sup>2</sup>	Heart rate per min.	Pulmonary artery pressure s/d, m mm. Hg	Brachial artery pressure s/d, m mm. Hg	Arterial blood O <sub>2</sub> sat. %	Cardiac output L./min./M. <sup>2</sup>	Heart rate per min.	Pulmonary artery pressure s/d, m mm. Hg	Brachial artery pressure s/d, m mm. Hg
O.S.	98	4.62	88	21/9, 15	130/79, 99	66	5.26	96	33/17, 24	122/68, 89
A.P.	95	3.26	83	12/6, 9	—	70	3.68	83	19/11, 15	—
W.M.	96	3.41	83	28/11, 18	144/76, 105	74	4.87	93	30/12, 20	145/80, 110
H.P.	95	2.86	80	22/11, 16	123/68, 98	76	3.22	88	27/12, 20	—
H.M.	98	2.63	67	27/11, 18	—	78	3.43	78	48/18, 31	—
G.H.	98	3.88	82	13/7, 10	122/78, 98	84	4.08	96	18/9, 15	125/82, 102
E.J.	95	4.30	80	16/6, 11	153/79, 109	85	4.68	92	21/9, 14	163/89, 122
C.D.	95	2.78	73	18/9, 13	132/79, 102	86	4.01	75	18/9, 13	130/78, 102
B.J.	98	3.43	78	20/10, 14	125/68, 86	87	3.43	79	23/11, 17	125/71, 92
F.D.	97	3.35	83	18/8, 13	127/72, 95	89	4.39	88	17/7, 12	117/66, 88
Average	97	3.45	80	20/9, 14	132/75, 99	80	4.11	87	25/12, 18	132/77, 101

at the alveolar-capillary level. To facilitate re-equilibration after change in the composition of inspired gas, a period of 15 to 25 minutes was allowed to elapse between the time of introduction of the new inspired mixture and the start of collection of blood and expired gas samples. Two consecutive measurements of blood flow were made in rapid succession after equilibration with each inspired gas mixture. The specific hypoxic mixture administered was selected on the basis of prior performance with hypoxic mixtures. Thus, whereas 6 subjects in table 1 (G.H., H.P., H.M.,

O.S., W.M., and A.P.) were able to fulfill the criteria for the steady state while breathing a mixture of 12 per cent oxygen in nitrogen, 4 (B.J., E.J., F.D., and C.D.) required a 14 per cent oxygen mixture.

The graded exercises were performed with the subject in the supine position, breathing ambient air. The exercise consisted of the alternate flexion and extension of each leg in time with a metronome, thereby moving, with each stroke, an attached leg weight through a fixed distance. Various weights and frequency of leg motion

Table 3

Relation between the Degree of Systemic Hypoxia and Pulmonary Artery Blood Flow and Pressure in Ten Normal Subjects

Number of subjects	Arterial blood O <sub>2</sub> sat. during hypoxia %	Average increase in cardiac output %	Average increase in pulmonary artery pressure mm. Hg
6	<85	19	7
4	>85	19	1

were used; these were selected, on the basis of prior performance, so as to double or triple the resting oxygen uptake. At least 5 minutes of stable exercise were allowed to elapse before collection of the samples necessary for measurement of pulmonary blood flow. The second level of exercise followed the first without interruption; an increase in work was accomplished by adding weights to each pulley system and by accelerating the frequency of leg strokes. Objective evidence for the accomplishment of the steady state included stabilization of the heart rate and  $\dot{V}_E$  by the end of the exercise period, and a value for  $R_E$  of approximately 1.0 during the collection period.

Blood and gas samples were drawn anaerobically. The blood samples were analyzed in rapid succession for oxygen content and capacity, and carbon dioxide content by the method of Van Slyke and Neill; the latter data, in conjunction with the arterial blood pH determined by a McInnes-Belcher glass electrode and the line charts of Van Slyke and Sendroy, were used for the calculation of arterial blood  $P_{CO_2}$ . The gas samples were analyzed for their oxygen and carbon dioxide content, by means of a micro-Scholander 0.5-ml. analyzer. All samples were required to check in duplicate, i.e., within 0.2 volume per cent for expired gases and 0.01 unit for pH.

### Subjects

The subjects will be considered according to the experiments in which they participated:

1. *Acute Bilateral Hypoxia.* Ten subjects, (tables 1-3), either entirely free of heart and lung disease, or with minimal tuberculous lesions, were included in this group. In these experiments, 2 separate control periods were followed by 2 successive periods of hypoxia.

2. *Graded Exercise.* Three of the 10 subjects (E.J., H.P., and G.H.) and 4 others (tables 4 and 5) underwent 2 consecutive periods of graded exercise following 2 control periods at rest; 1 of these subjects (G.H.) was slightly anemic (table 5).

3. *Graded Exercise Followed by Acute Hypoxia.* In 3 of the subjects (B.J., H.P., and G.H.), the periods of exercise were followed in succession by a period of rest, an additional period of breathing ambient air, and a final period during which a hypoxic mixture was breathed (tables 2 and 3). For the sake of comparison, 3 patients with restricted vascular beds were studied in a similar fashion: 2 (W.E. and L.O.) had undergone pneumonectomy for unilateral suppurative disease; 1 (A.G.) suffered from chronic obstructive pulmonary emphysema (table 6).

4. *Bilateral Stellate Ganglionectomy.* In 1 subject (H.P.) the above sequence of exercise and hypoxia was repeated following bilateral stellate and upper thoracic (T-1 to T-4) ganglionectomy for Raynaud's syndrome; the operation on the right side also included resection of the middle cervical ganglion and T-5.

### Results

#### Observations on the Effects of Acute Bilateral Hypoxia

##### Ventilation and Gas Exchange

The changes in minute ventilation ( $\dot{V}_E$ ), oxygen uptake ( $\dot{V}_{O_2}$ ) and respiratory exchange ratio ( $R_E$ ) for 10 subjects during low-oxygen breathing are listed in table 1. Each value in this table is the average of 2 consecutive periods. The average increment in  $\dot{V}_E$  was 22 per cent and in  $\dot{V}_{O_2}$  was 6 per cent. The average increase in  $R_E$  during the hypoxic periods was .05.

##### Arterial Blood Oxyhemoglobin Saturation ( $Sa_{O_2}$ )

In table 2, the patients are listed according to the level of  $Sa_{O_2}$  that obtained during acute hypoxia. As may be seen in this table, the  $Sa_{O_2}$  during the breathing of ambient air averaged 97 per cent; during low-oxygen breathing, the  $Sa_{O_2}$  ranged from 89 to 66 per cent.

##### Cardiac Output

As may also be seen in table 2, the cardiac outputs during breathing of ambient air were within normal limits in all but 2 subjects (O.S. and E.J.) in whom they were slightly elevated; during low-oxygen breathing there was an average increase of 19 per cent; this increase is statistically significant ( $p < .01$ ). The relation between the decrease in arterial oxygen saturation and the increase in cardiac output is illustrated in figure 1. In all but 2

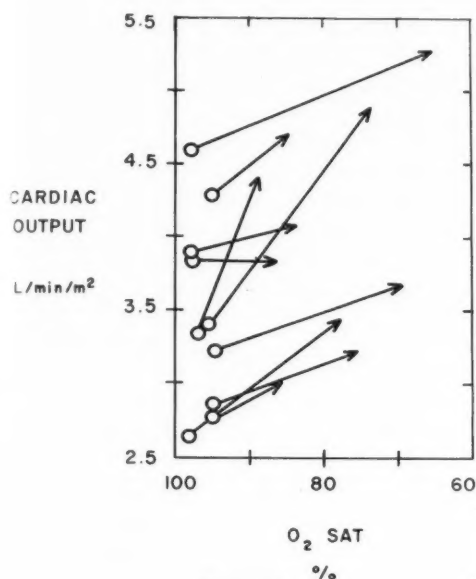


Figure 1

The relationship between the change in the oxy-hemoglobin saturation of arterial blood and the change in cardiac output in 10 normal subjects. The control values appear as circles; the values during acute hypoxemia are represented by the tips of the arrows. In general, the cardiac output increased during systemic arterial hypoxemia.

of the patients (B.J. and E.J.), the increment in cardiac output exceeded 9 per cent, a value previously established in this laboratory as

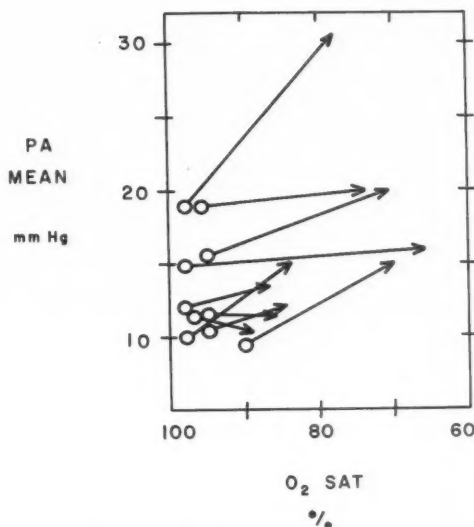


Figure 2

The relationship between the change in the oxy-hemoglobin saturation of arterial blood and the change in pulmonary arterial mean blood pressure. Symbols as in figure 1. In general, the pulmonary arterial blood pressure increased during systemic arterial hypoxemia.

the upper limit of normal variation between consecutive measurements during the breathing of ambient air.<sup>10</sup>

Table 4

Changes in Ventilation and Gas Exchange during Graded Exercise in Seven Normal Subjects

Subject	Age, yrs.	Sex	BSA M. <sup>2</sup>	Rest			Exercise 1			Exercise 2		
				$\dot{V}_E$ L./min./M. <sup>2</sup>	$\dot{V}_{O_2}$ ml./min./M. <sup>2</sup>	R <sub>E</sub>	$\dot{V}_E$ L./min./M. <sup>2</sup>	$\dot{V}_{O_2}$ ml./min./M. <sup>2</sup>	R <sub>E</sub>	$\dot{V}_E$ L./min./M. <sup>2</sup>	$\dot{V}_{O_2}$ ml./min./M. <sup>2</sup>	R <sub>E</sub>
B.B.	25	M	1.77	3.53	144	.79	6.37	280	.88	10.10	403	.96
B.J.	25	M	1.88	4.18	147	.84	7.24	303	.85	8.30	352	.86
B.C.	49	M	1.80	4.11	125	.88	9.24	283	.94	27.60	606*	1.13
B.C.	36	F	1.63	2.37	111	.75	3.72	166	.78	7.72	298	.91
B.P.	44	F	1.56	4.61	125	.81	7.16	222	.82	10.65	301	.89
B.M.	28	M	1.51	3.59	123	.89	9.42	260*	1.04	16.90	466*	1.13
B.H.	35	F	1.54	4.25	140	.84	5.35	191	.85	6.95	257	.87
Average				3.80	131	.83	6.93	243	.88	12.60	383	.96

\*Values for  $\dot{V}_{O_2}$  are approximate due to high respiratory exchange ratios.

Table 5  
Effects of Graded Exercise on Cardiac Output, Pulmonary and Systemic Artery Blood Pressures in Seven Normal Subjects

Subject	Rest					Exercise 1					Exercise 2				
	O <sub>2</sub> capacity ml./100 ml.	Cardiac output L./min./M <sup>2</sup>	Heart rate per min.	Pulmonary artery pressure s/d, m mm. Hg	Brachial artery pressure s/d, m mm. Hg	Cardiac output L./min./M <sup>2</sup>	Heart rate per min.	Pulmonary artery pressure s/d, m mm. Hg	Brachial artery pressure s/d, m mm. Hg	Cardiac output L./min./M <sup>2</sup>	Heart rate per min.	Pulmonary artery pressure s/d, m mm. Hg	Brachial artery pressure s/d, m mm. Hg	Cardiac output L./min./M <sup>2</sup>	Heart rate per min.
J.B.	20.2	4.14	74	23/9, 16	113/61, 83	5.01	98	24/13, 19	125/69, 91	5.60	104	25/10, 18	123/69, 89	5.60	104
B.J.	19.5	3.43	78	20/10, 14	125/68, 86	5.43	90	25/12, 18	139/73, 95	5.70	96	22/11, 17	140/72, 99	5.70	96
J.C.	18.5	2.85	73	20/9, 14	141/80, 109	4.29	100	21/9, 15	—	*	140	22/12, 18	—	*	140
D.C.	17.3	—	80	17/7, 12	104/71, 88	3.13	90	23/10, 17	104/71, 90	4.97	90	23/9, 16	112/74, 95	4.97	90
H.P.	17.1	2.98	80	22/11, 16	123/68, 98	3.98	97	26/14, 20	132/75, 105	4.36	107	27/13, 20	135/77, 109	4.36	107
M.M.	15.8	3.58	84	14/7, 11	119/91, 104	*	108	13/8, 11	121/86, 106	*	130	13/8, 12	142/84, 107	*	130
G.H.	14.3	3.50	82	13/7, 10	122/78, 98	4.48	102	16/7, 12	128/83, 105	4.76	110	17/8, 14	123/81, 102	4.76	110
Average		(3.41)	79	18/9, 13	121/74, 95	(4.29)	98	21/10, 16	125/76, 99	(5.01)	111	21/10, 16	129/76, 100	(5.01)	111

\*Values are not calculated by Fick equation owing to high R<sub>a</sub>; see table 4.

#### Pulmonary Artery Pressure

Figure 2 illustrates that, in general, the pulmonary arterial pressure increased during systemic hypoxemia. As may be seen in table 2, during hypoxia the average pulmonary arterial pressure rose from control values of 20/9, with a mean of 14 mm. Hg to 25/12, with a mean of 18 mm. Hg; the peak pressures were achieved gradually in the first few minutes of low-oxygen breathing and then maintained. These increases were statistically significant ( $p < .01$ ). The greater part of the rise in mean pressure was due to the rise in systolic pressure. In table 3 it can be seen that as long as the Sa<sub>o<sub>2</sub></sub> exceeded 85 per cent, the pulmonary arterial pressure remained at control levels; on the other hand, a drop in Sa<sub>o<sub>2</sub></sub> to below 85 per cent was associated with a rise in pressure. Figure 3 indicates that an increase in pulmonary arterial pressure was consistently associated with an increase in cardiac output.

#### Brachial Artery Pressure

There was no consistent pattern of change in systemic blood pressures during hypoxia and average blood pressures for the entire group remained unchanged.

#### Observations on the Effects of Graded Exercise

##### Ventilation and Gas Exchange

The minute ventilation ( $\dot{V}_E$ ), oxygen uptake ( $\dot{V}_{O_2}$ ) and respiratory exchange ratios ( $R_E$ ) for the control and exercise periods are listed in table 4. As may be calculated from these data, the average oxygen uptake almost doubled (+85 per cent) during the first level of exercise and almost tripled (+192 per cent) during the second level. The ventilation ( $\dot{V}_E$ ) and carbon dioxide output kept pace with the augmented metabolic activity as reflected in near-normal values for the respiratory exchange ratio ( $R_E$ ).

##### Arterial Blood Oxyhemoglobin Saturation

In all of these subjects, the arterial blood oxyhemoglobin saturation was normal at rest (95 to 98 per cent) and remained either unchanged or increased during exercise.

Table 6

*Pulmonary Artery Blood Flows and Pressures during Acute Hypoxia and Exercise in Three Patients with Restricted Vascular Beds Studied during the "Steady State"*

Subject	Diagnosis	Cardiac output				Pulmonary artery mean pressure			
		Control L./min./M. <sup>2</sup>	Hypoxia* L./min./M. <sup>2</sup>	Exercise 1† L./min./M. <sup>2</sup>	Exercise 2 L./min./M. <sup>2</sup>	Control mm. Hg	Hypoxia* mm. Hg	Exercise 1 mm. Hg	Exercise 2 mm. Hg
W.E.	1 normal lung	2.77	3.54	3.20	4.06	16	21	20	24
L.O.	1 normal lung	3.01	3.48	3.79	3.73	15	18	20	20
A.G.	Chronic obstructive emphysema	3.42	3.75	3.94	4.40	17	21	21	26

\*All subjects breathed 12 per cent O<sub>2</sub> in N<sub>2</sub>; the arterial blood O<sub>2</sub> saturations were 73, 71, and 81 per cent, respectively.

†During exercise, subjects W.E. and L.O. maintained 96 to 98 per cent O<sub>2</sub> saturation in arterial blood while breathing ambient air; subject A.G. was given 25 per cent O<sub>2</sub> in N<sub>2</sub> as the inspired mixture during exercise to maintain 96 per cent O<sub>2</sub> saturation.

#### Cardiac Output

The measurement of the resting cardiac output was inadvertently omitted in 1 subject (D.C.). In the other subjects of table 5, the cardiac outputs were either normal or slightly high at rest. During exercise, the cardiac outputs increased normally, approximately 1 liter increase in flow per 0.1 liter increase in oxygen uptake.

#### Pulmonary Artery Pressures

As indicated in table 5, pulmonary artery mean pressures were normal at rest and increased, on the average, by 3 mm. Hg during the first exercise period; the increment in mean pressure was associated with a rise in systolic pressure of 3 mm. Hg without change in diastolic pressure. Despite another increment in cardiac output during the second exercise period, there was, on the average, no further increase in pressure. In figure 4 is illustrated the relation between the successive increments in cardiac output and the pulmonary artery pressure. It is clear from a consideration of tables 2 and 5 that, despite larger blood flows, exercise was associated with lower pulmonary artery pressures than was hypoxia.

A distinction also exists not only in the final levels of pulmonary artery pressure, but also in the patterns of change. During

hypoxia, there was a gradual rise in pulmonary artery pressure, generally requiring 1 to 3 minutes to achieve the peak, followed by a plateau; this pattern presumably reflects the gradual reduction in the level of alveolar oxygen tension following acute exposure to a low-oxygen mixture. On the other hand, 2 different patterns were noted in the 3 subjects who manifested an appreciable rise in mean pulmonary artery pressure during the first period of exercise; thus 2 (B.J. and H.P.) reached peak pressures within 15 to 30 seconds following the start of exercise, whereas 1 (D.C.) required 2 minutes to achieve peak levels. The changes in pressure were documented by continuous pressure tracings recorded during rest, exercise, rest, and hypoxia. The contrasting pattern between the abrupt increment during exercise and the gradual increment during hypoxia is illustrated for subject H.P. in figure 5; this figure also illustrates the general pattern of pulmonary arterial pressures during the second exercise period.

In the subjects who manifested an abrupt rise in pulmonary artery pressure with the start of exercise, an attempt was made to assess indirectly the role of an increment in pulmonary blood volume in effecting this

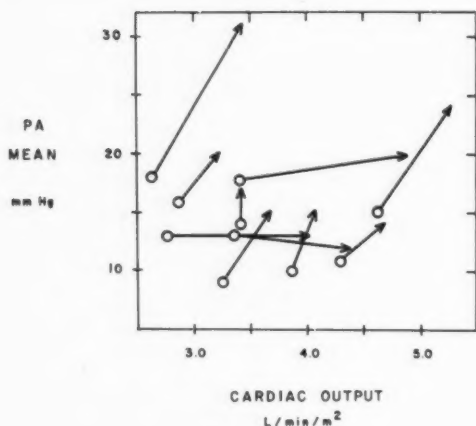


Figure 3

The relationship between the change in cardiac output and the change in mean pulmonary arterial blood pressure during acute hypoxia. Symbols as in figure 1. Increases in mean pulmonary arterial blood pressure were consistently associated with increases in cardiac output.

increase: the legs were suddenly but passively raised while the subjects maintained an uninterrupted breathing pattern under pneumotachygraphic control. In neither of these subjects did this maneuver elicit a rise in pulmonary artery pressure.

#### Brachial Artery Pressures

As may be seen in table 5, brachial artery pressures were normal at rest, and increased somewhat during the successive periods of graded exercise.

#### Observations on the Effects of Acute Bilateral Hypoxia and of Graded Exercise in the Same Subjects

In order to compare the effects of acute hypoxia and graded exercise in the same subjects, 3 normal subjects (B.J., G.H., and H.P.) and 3 patients with restricted vascular beds (W.E., L.O., and A.G.) were subjected to acute hypoxia after 2 consecutive periods of exercise and a second control period. The data for the normal subjects are contained in tables 1, 2, 4, and 5; the pertinent data for the 3 patients are listed in table 6. At equivalent levels of cardiac output, the normal subjects manifested higher pulmonary artery pressures during hypoxia than during exercise (fig. 6); on the other hand, in the

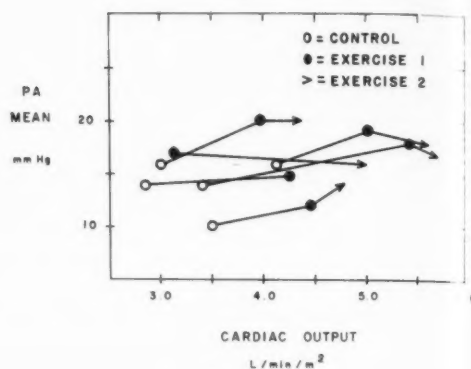


Figure 4

The relationship between the change in cardiac output and the change in mean pulmonary arterial blood pressure during graded exercise. Progressive increases in cardiac output during graded exercise were not associated with corresponding increments in pulmonary arterial blood pressures.

patients, equal increments in blood flow, regardless of their induction by either exercise or hypoxia, elicited linear and equivalent increments in pulmonary artery pressure.

In the 3 normal subjects, similar mixed venous blood oxygen tensions obtained during one level of the graded exercise and during acute hypoxia. Although the blood entering the lungs during these 2 experimental situations is similar with respect to oxygen tension, actually the areas of the vascular bed affected by the hypoxic stimulus differ considerably. Thus, as may be seen in figure 7, hypoxia induced by airway affects the entire pulmonary vascular tree, whereas, during exercise, the hypoxia of the mixed venous blood is confined almost exclusively to the pre-capillary bed, since hypoxia is abolished promptly once the blood enters the pulmonary capillary bed. In these subjects, despite the same mixed venous oxygen tensions, the larger blood flows during exercise were associated with lower pulmonary artery mean pressures than during acute hypoxia.

#### Observations on the Effects of Bilateral Stellate Ganglionectomy

The observations on patient H.P. during exercise and acute hypoxia were repeated 6 weeks following partial cervicodorsal symp-

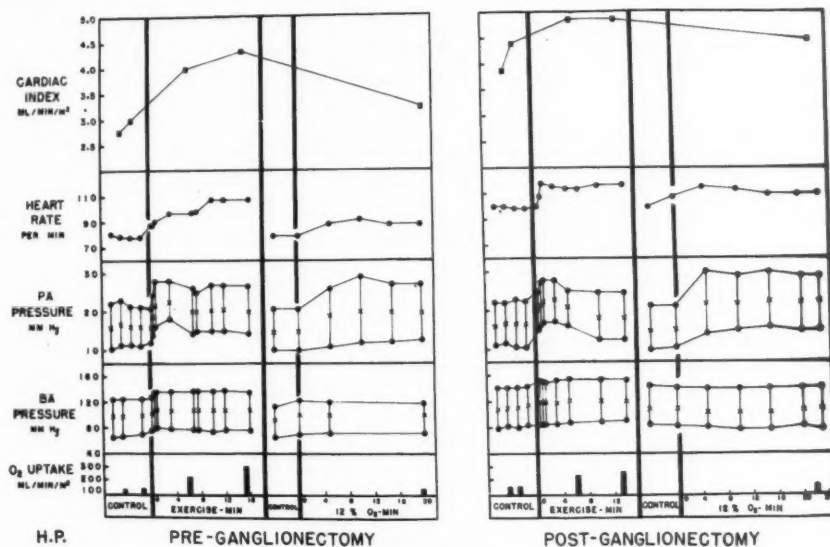


Figure 5

The circulatory responses of subject H.P. to graded exercise and to acute hypoxia before and after extensive bilateral sympathetic ganglionectomy. The pattern of response in the pulmonary circulation was not altered by the surgical procedure.

theectomy for Raynaud's syndrome. The circulatory responses prior to and following ganglionectomy are illustrated in figure 5. The preoperative measurements, particularly the abrupt rise in pulmonary artery pressure with the onset of exercise, as contrasted with the gradual increase during hypoxia, have already been noted. Similarly, the inordinate increment in pressure during acute hypoxia for the increment in blood flow has also been mentioned. Following sympathectomy, despite somewhat higher original levels of blood flow, the general pattern of response to both acute hypoxia and exercise remained unchanged.

#### Discussion

The present paper is concerned with the factors that determine pressure-flow relationships in the pulmonary circulation during acute hypoxia and exercise. The results support the view that the contribution of an increase in pulmonary blood flow to this response is small and also provide some evidence that the sympathetic ganglia are not essential for the pressor effect. They leave for other

studies<sup>11-13</sup> to establish if, and how, local hypoxia affects the different pulmonary vascular segments.

#### Relationship of the Increase in Pulmonary Blood Flow to the Rise in Pulmonary Arterial Blood Pressure during Acute Hypoxia

It is now well known that the pressure-flow relationship of the normal pulmonary artery tree is such that an appreciable increase in pulmonary blood flow is accommodated with only a barely perceptible increment in pulmonary arterial blood pressure.<sup>14-22</sup> In the present study, blood flow was measured by the Fick principle in such a way as to avoid the multiplicity of potential errors.<sup>25-27</sup> By comparing the effects of graded exercise and acute hypoxia, particularly in the same subjects, it was possible to show that the increment in pulmonary blood flow during acute hypoxia is insufficient to account for the rise in pulmonary arterial blood pressure in normal subjects. By way of contrast, severe curtailment of the pulmonary vascular bed may so alter the pressure-flow characteristics of the lung that a slight increment in blood

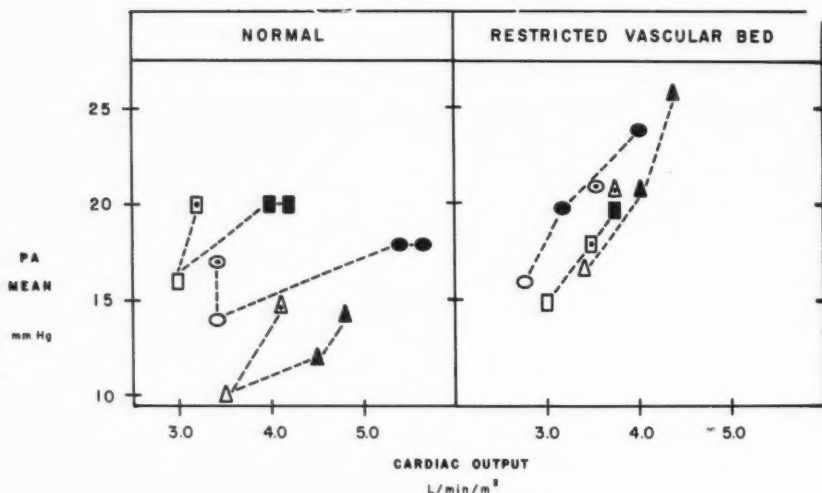


Figure 6

A comparison of the effect of an increase in cardiac output on the mean pulmonary arterial blood pressure during acute hypoxia and during graded exercise in normal subjects and in subjects with restricted pulmonary vascular beds. The control observations are represented by clear symbols; the observations during successive levels of exercise by solid symbols; the observations during hypoxia by the dotted symbols. In the normal subject during acute hypoxia, the mean pulmonary arterial blood pressure was higher for any particular cardiac output than during exercise. This distinction no longer obtains in subjects with restricted pulmonary vascular beds.

flow will elicit inordinate increments in pulmonary arterial blood pressure. It is of interest in this regard, that only under conditions of severe restriction of the pulmonary vascular bed may a linear relationship between blood pressure and flow exist. Moreover, under this circumstance, it would be expected that the pressor effect of mild vasomotor activity would be obscured by the mechanical effects of an increase in blood flow in a restricted vascular bed. Such observations emphasize that the pressure-flow curve must be established for each subject separately in order to interpret changes in pulmonary vascular resistance to blood flow.

The patterns of change in pulmonary blood flow during exercise are similar to those that have recently been described by others.<sup>19-21</sup> The present studies are in accord with these observations, both with respect to the time-sequence of changes and the relationship between oxygen uptake and cardiac output.

Furthermore, through the use of continuous records of pulmonary arterial blood pressure during exercise, the present studies support the view that the pulmonary arterial blood pressure rises slightly, but consistently, during exercise.<sup>18, 19, 21</sup> Of particular interest is the failure of the second level of exercise, with pulmonary blood flows of twice normal, to evoke a further rise in pulmonary arterial pressure in the normal subjects. The plateau in pressure may be related to widening of patent pulmonary vessels by the increased ventilatory efforts of exercise, to accelerated flow through the center of vessels of unchanged size or to opening of new vessels. These observations do not distinguish between these prospects.

#### Role of the Autonomic Nervous System in Mediating the Pulmonary Arterial Pressure Response to Acute Hypoxia

Others have implicated the sympathetic innervation of the lung, operating under the

Influence of the systemic chemoreceptors, in the genesis of the pulmonary hypertension of acute hypoxia.<sup>28</sup> In the present study of a subject with extensive sympathectomy for Raynaud's phenomena, the pattern of the pulmonary pressor response to acute hypoxia was indistinguishable from the normal. This type of response has since been duplicated in another patient with even more extensive sympathectomy.<sup>29</sup> These observations, particularly when coupled with others concerning the persistence of the pressor response following the administration of atropine,<sup>11, 12</sup> provide no support for the hypothesis that the autonomic nervous system is involved in the pulmonary hypertension of human subjects who are exposed to acute hypoxia.

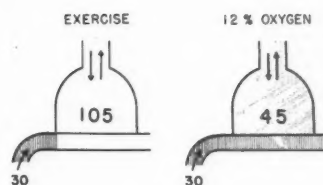
#### Other Mechanisms Involved in the Pressor Response to Acute Hypoxia

It is clear that the present study has sufficed mainly to exclude certain mechanical and nervous factors as prime movers in the pulmonary hypertensive response to acute hypoxia. In the accompanying paper, the role of the pulmonary blood volume is considered. The present study also suggests that the pulmonary pressor response to acute hypoxia involves a change in the distensibility and in the dimensions of some segment of the pulmonary vascular tree. Other studies, particularly those concerned with the relief, by acetylcholine, of the pulmonary hypertension of acute hypoxia<sup>24, 30, 31</sup> as well as that of chronic lung and heart disease<sup>32</sup> suggest that vasomotor activity may be involved in the pulmonary pressor response to acute hypoxia. However, the exact site and mode of action of the hypoxic stimulus remain to be uncovered.<sup>33, 34</sup>

#### Summary

The effects of acute hypoxia, of graded exercise, or both, on the pulmonary circulation were studied in 17 normal subjects. In 3 of these subjects, and in 3 patients with restricted vascular beds, the effects of these stimuli were compared during successive test periods.

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MEAN PA PRESSURE MM Hg	19	21
MEAN CARDIAC INDEX ML/MIN/M <sup>2</sup>	4.67	3.54

Figure 7

Mean pulmonary arterial pressure and flow in 4 normal subjects at same mixed venous  $pO_2$  during exercise and hypoxia. Schematic representation of the difference between the pulmonary vascular segments which are rendered hypoxic by exercise and by low-oxygen breathing.

In 7 normal subjects, moderate exercise, associated with an increase in cardiac output of approximately 25 per cent, resulted in an average rise in pulmonary arterial mean pressure of 3 mm.Hg. More strenuous exercise in the same subjects, associated with a further increase in cardiac output of approximately 25 per cent, did not elicit further increment in pulmonary arterial mean pressure.

In contrast, 10 subjects with normal pulmonary circulations, who responded to acute hypoxia with an average reduction of arterial oxygen saturation of 17 per cent, manifested an average increase in cardiac output of 5 per cent and an average rise in mean pulmonary arterial pressure of 4 mm.Hg. The critical level of arterial blood oxygen saturation for a significant rise in pulmonary arterial pressure was 85 per cent: in 6 subjects, with arterial blood  $O_2$  saturation reduced below this level, the average pulmonary artery pressure rise was 7 mm. Hg.

In the 3 subjects with normal pulmonary circulations who performed exercise and were exposed to acute hypoxia, the contrasting effects of these stimuli on the pulmonary circulation were striking. In the 3 patients with restricted vascular beds exposed successively to both stimuli, the rise in pulmonary arterial mean pressure appeared to be linearly

related to the increase in pulmonary blood flow.

In 1 subject, the surgical resection of the preganglionic fibers and ganglia which supply sympathetic efferent nerves to the pulmonary vascular tree was without effect on the responses of the pulmonary circulation to acute hypoxia and to exercise.

The present study failed to identify the mechanism and the site of action of acute hypoxia on the pulmonary circulation.

#### Summario in Interlingua

Le effectos de acute hypoxia, de graduate exercitio, e de un combination del duo super le circulation pulmonar esseva studiate in 17 subjectos normal. In 3 de iste subjectos e in 3 patientes con restringite vasculatura le effectos del mentionate stimulus esseva comparate durante successive periodos de testation.

In 7 normales, moderate formas de exercitio—associate con un augmento del rendimento cardiac de approximativemente 25 pro cento—resultava in un augmento medie del tension pulmono-arterial medie de 3 mm de Hg. Plus intense formas de exercitio in le mesme subjectos—associate con un augmento additional del rendimento cardiac de de novo approximativemente 25 pro cento—non evocava ulle augmento additional in le tension pulmono-arterial medie.

Per contrasto con isto, 10 subjectos con normalitate del circulation pulmonar—qui respondeva a acute hypoxia per un reduction medie del saturation oxygenic in le sanguine arterial de 17 pro cento—manifestava un augmento medie del rendimento cardiac de 5 pro cento e un augmento medie del tension pulmono-arterial medie de 4 mm de Hg. Le nivello critic de saturation oxygenic in le sanguine arterial pro un augmento significative del tension pulmono-arterial esseva 85 pro cento. In 6 subjectos in qui le saturation oxygenic in le sanguine arterial esseva reduceite a infra le nivello critic de 85 pro cento, le augmento medie del tension pulmono-arterial amontava a 7 mm de Hg.

In le 3 subjectos qui habeva normal circulationes pulmonar e qui esseva subjicite a exercitio e hypoxia, le effectos contrari de iste duo stimulus in le circulation pulmonar esseva frappante. In le 3 patientes con restringite vasculaturas, le exposition successive a ille duo stimulus produceva un augmento del tension pulmono-arterial medie que pareva esser relationate linearmente al augmento del fluxo de sanguine pulmonar.

In 1 subjecto, le resection chirurgie del fibras preganglionic e del gangliones que provide efferent nervos sympathic al vasculatura pulmonar remaneva

sin effecto super le responsas del circulation pulmonar a acute hypoxia e a exercitio.

Le presente studio non resultava in un identification del mechanismo e del sito de action del effecto de acute hypoxia super le circulation pulmonar.

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# Effects of Acute Hypoxia on the Volume of Blood in the Thorax

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E. W. BRAUNWALD, M.D., AND A. P. FISHMAN, M.D.

**T**HE RESULTS presented in the first paper of this series confirm the observations of others that acute hypoxia frequently raises the pulmonary arterial pressure in normal man. This pressor effect cannot be solely attributed to an augmented cardiac output, nor can it be ascribed to an elevated left atrial pressure. It seems, therefore, to arise from a change in the dimensions of some portion or portions of the pulmonary vascular bed.

Whether this change involves an alteration in the pulmonary blood volume has not been settled, since experiments in man and in animals have yielded conflicting results.<sup>1-8</sup> The present study was designed to investigate the relation between volume and pressure by using two dissimilar methods. The first entailed measuring the central blood volume before and during hypoxia; the second involved recording the change in the relative weights of the two ends of the body when hypoxia was induced.

## Methods

### Measurement of Central Blood Volume

The central blood volume was measured by using the dye-dilution method of Hamilton.<sup>9</sup> For this purpose, a no.-8 cardiac catheter was advanced until its tip lay in the main pulmonary artery and a Cournand needle was inserted into the right brachial artery. The patient was then allowed to rest for 15 minutes before observations were begun.

The experimental protocol comprised 2 20-

minute breathing periods, separated by a 10-minute interval of rest. Eight of the 25 patients breathed 21 per cent oxygen during both periods; the remaining 17 breathed 21 per cent oxygen during the first and either 14 per cent or 12 per cent oxygen during the second period.

Pressures were recorded at 2-minute intervals from the pulmonary and brachial arteries. At the eighteenth minute, 4 ml. of Evans blue dye were rapidly injected through the catheter into the pulmonary artery. A dilution curve was inscribed from the brachial artery by withdrawing blood at a constant rate of 0.5 ml. per second through a Colson densitometer. The concentration of dye in plasma was read in a Beckman Model DU spectrophotometer. This value was used to calibrate the dye curve according to the pooled-sample method of McNeeley and Gravelle.<sup>10</sup> The calibrated curve, used in conjunction with the formulas of Hamilton,<sup>9</sup> and after allowance was made for the amount of dye retained in the catheter, provided estimates of the cardiac output, the mean circulation time, and the central blood volume.

### Determination of Distribution of Weight

For these studies, each subject lay supine on a teeter-board constructed of light-weight pine and plywood.<sup>11, 12</sup> The board was balanced on a fulcrum which could be adjusted to the approximate horizontal level of the center of gravity of the combined mass of the board and the subject (fig. 1). A spring held the board in position; it had a linear coefficient of elasticity over the range of motion involved in the experiments. A dashpot filled with mineral oil damped the rapid oscillations caused by the respiratory movements of the chest and abdomen, and by the beating of the heart. The balance of the board was such that a 50-Gm. weight placed 10 cm. from the fulcrum deflected the kymograph pen approximately 1 cm.

Each subject lay on the board for approximately 2 hours. During the first hour no observations were recorded because experience indicated that this was a minimal period for the 2 ends of the body to attain stable weights.<sup>11, 13</sup> To ensure that stability had been achieved by the end of the hour, 3 records were obtained at 10-minute intervals. The subject then breathed 21 per cent

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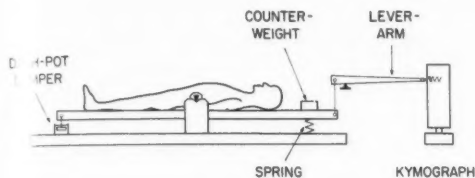


Figure 1

Schematic drawing of a teeter-board.

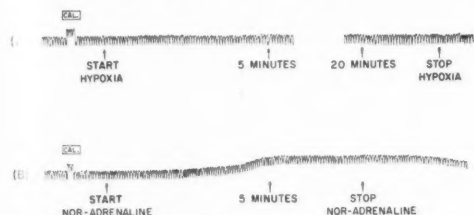


Figure 2

Effect of (A) hypoxia and (B) norepinephrine on the relative weights of the 2 ends of the body. Response marked CAL indicates effect of placing a 50-Gm. weight 10 cm. from fulcrum on head-end of the board.

oxygen through a mouthpiece for 20 minutes while a continuous tracing of the kymograph pen was recorded and a sample of arterial blood was collected. At the end of this period, the 21 per cent oxygen mixture was replaced by one containing 12 per cent oxygen. The tracing was again recorded and, after 20 minutes of hypoxia, another sample of arterial blood was drawn. In the majority of the subjects the hypoxic period was followed by a second control period. A typical tracing is reproduced in figure 2A.

### Subjects

All subjects were either normal laboratory workers or convalescent patients without cardiac or pulmonary disease. Each had fasted for 12 hours before the study. None received premedication.

### Results

#### Subjects in Whom Two Measurements of Central Blood Volume Were Made While They Breathed Ambient Air

The studies in these 8 patients were designed to test the reproducibility of the measurement of the central blood volume in persons lying quietly at rest. Although the average of the volumes measured in the first breathing period was virtually identical with the average of the volumes measured in the second, our data, like those of Doyle, Wilson, Lévine, and Warren,<sup>14</sup> demonstrated consid-

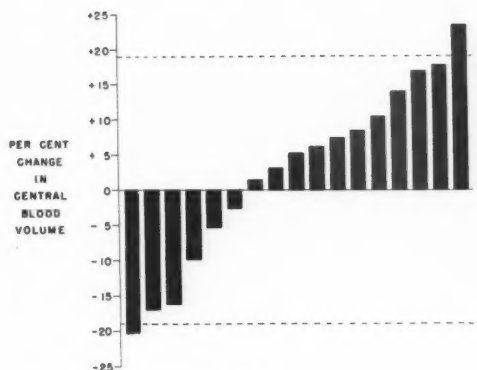


Figure 3

Effect of hypoxia on central blood volume.

erable variation between the 2 measurements in individual patients. When the difference between the volumes measured in each patient was divided by the first volume, the range extended from -11 to +12.6 per cent, with an average difference of -1.9 per cent. With the assumption that these differences had a Gaussian distribution, their standard deviation was 7.33 per cent. Hence, 2.58 standard deviations, the number necessary to include 99 per cent of the observations, was  $\pm 18.91$  per cent.

#### Patients in Whom the Central Blood Volume Was Measured before and during Hypoxia

The volumes measured in the 17 patients who were made hypoxic are recorded in table 1. The values obtained while they breathed 21 per cent oxygen gave an average volume of 0.79 L./M.<sup>2</sup>, and a standard deviation of 0.119 L./M.<sup>2</sup>. The volumes measured during hypoxia gave an average value of 0.81, and a standard deviation of 0.566 L./M.<sup>2</sup>. When analyzed by the "t" test of Fisher, the difference between the averages was not significant ( $p > .10$ ).

The changes in volume are depicted graphically in figure 3. Each bar represents a single patient. The length of the bar represents the percentage change in volume calculated as the difference between the ambient air and hypoxic values divided by the ambient air value. In only 2 patients (J.O'C. and J.H.) did the percentage change exceed the limits

Table 1

*Changes in Arterial Blood Oxyhemoglobin Saturation, Pulmonary Arterial Pressure, Cardiac Index, Mean Circulation Time, and Central Blood Volume during Acute Hypoxia in Seventeen Normal Subjects*

Subject	Breathing mixture: Ambient air					Breathing mixture: 12-14% O <sub>2</sub> in N <sub>2</sub>				
	Arterial blood O <sub>2</sub> sat. %	Pulmonary arterial pressure s/d.m mm. Hg	Cardiac output L./min./M. <sup>2</sup>	Mean circulation time sec.	Central blood volume L./M. <sup>2</sup>	Arterial blood O <sub>2</sub> sat. %	Pulmonary arterial pressure s/d.m mm. Hg	Cardiac output L./min./M. <sup>2</sup>	Mean circulation time sec.	Central blood volume L./M. <sup>2</sup>
J.O.	98	19/6,12	4.1	10.9	.74	90	20/8,14	3.6	11.7	.70
C.D.	93	18/9,13	3.0	12.8	.64	88	18/9,13	3.2	12.3	.66
J.O'C.	91	26/10,16	4.5	14.1	1.06	86	33/14,22	5.3	14.8	1.31
P.M.	95	12/5,9	3.4	12.2	.69	85	16/7,11	4.7	8.9	.70
M.B.	94	16/6,9	3.3	15.2	.84	83	18/7,12	3.9	14.0	.91
E.J.	98	20/7,12	3.0	14.8	.74	83	29/10,18	3.9	11.0	.72
A.O.	95	22/9,15	4.8	12.1	.97	80	23/10,15	6.9	8.9	1.02
C.G.	98	18/8,13	4.3	11.1	.80	79	24/11,17	4.1	12.4	.85
J.L.	94	23/12,18	3.5	11.7	.68	76	26/12,19	4.5	9.7	.73
W.M.	96	28/11,18	3.5	13.0	.76	74	30/12,20	4.6	11.5	.88
V.P.	95	20/9,14	4.7	9.9	.78	74	22/14,18	5.1	10.5	.89
H.C.	95	22/8,14	3.5	10.7	.62	72	40/14,27	3.6	8.7	.52
J.H.	98	19/9,14	3.2	14.8	.79	71	33/19,26	3.2	11.9	.63
A.P.	93	13/6,10	4.1	14.8	1.01	70	19/11,15	5.2	10.5	.91
A.C.	96	21/9,15	4.1	11.1	.76	68	34/17,24	5.8	8.7	.84
O.S.	97	22/10,16	4.3	10.9	.78	66	33/18,25	5.9	9.4	.92
G.Y.	96	24/11,16	4.6	9.2	.71	65	31/14,22	5.1	6.9	.59
Average	95	20/9,14	3.9	12.3	.79	77	26/12,19	4.6	10.7	.81

of  $\pm 18.91$  per cent calculated for all 8 subjects.

Despite the lack of change in the central blood volume, hypoxia exhibited its usual pressor effect on the pulmonary arterial pressure. Thus, the average value during the control period was 13.7 mm. Hg and during the period of hypoxia it rose to 18.7 mm. Hg. This difference would have arisen by chance less frequently than 1 in 100 times ( $p < .01$ ).

#### Patients Studied on the Teeter-Board

None of the 9 patients studied on the teeter-board demonstrated any change in the position of the center of gravity during hypoxia, despite the fact that arterial saturations as low as 62 per cent were induced. A typical record is shown in figure 2A, and is contrasted with a tracing recorded during an infusion of norepinephrine (fig. 2B). In the latter instance, the center of gravity shifted toward the head-end of the body.

#### Discussion

In the studies reported in the preceding paper, the cardiac output was measured by the Fick principle and the importance of the steady-state was emphasized. In the present studies, the cardiac output was measured by the dilution principle and safeguards of the same sort were applied. The most frequent difficulty was imposed by an unstable densitometer baseline during the hypoxic period. This unsteadiness was caused by variations in the oxygen saturation of the blood in the systemic arteries, and in 12 patients the fluctuations were so large that the data were discarded. In the patients included in this report, baselines recorded over a period of 20 seconds showed variations that were less than 5 per cent of the maximum height of the curve.

The central blood volume as measured in these studies included not only the blood in

the pulmonary vessels, but that contained in the chambers of the left heart and that segment of the aorta and its branches that lay at points temporally equidistant from the aortic valve. In keeping with the observations of Doyle, Wilson, and Warren,<sup>5</sup> our results indicated that hypoxia did not alter this volume of blood.

Furthermore, no shift in the center of gravity could be demonstrated when hypoxia was induced in patients lying on the teeter-board. These results confirm and extend earlier observations from this laboratory<sup>15</sup> and agree with those published by Honig and Tenney.<sup>8</sup> According to the calibration, the teeter-board would have disclosed a change in the pulmonary blood volume of 50 ml. or less, if the blood moved through a distance of 10 cm. along the length of the body. These observations support the measurements of the central blood volume in indicating that the volume of blood in the thorax does not change appreciably during hypoxia.

#### Summary

Two different methods were used to study the effect of acute hypoxia on the volume of blood in the thorax. The first method entailed estimating the central blood volume by the Stewart-Hamilton dye-dilution technic; the second involved the use of a teeter-board. The 2 methods gave comparable results. Both indicated that the volume of blood in the thorax is not appreciably altered by hypoxia.

#### Summario in Interlingua

Duo differente methodos esseva usate pro studiar le effecto de hypoxia acute super le volumine del sanguine in le thorace. Le prime del duo methodos consisteva in estimar le volumine de sanguine central per medio del technica a dilution de colorante secundo Stewart-Hamilton; le secunde utilisava un planca basculante. Le resultatos obtenite per le duo methodos esseva comparabile. Ambes indicava que le volumine de sanguine in le thorace non es alterate appreciabilemente per le effectos de hypoxia.

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# Effects of Breathing Carbon Dioxide upon the Pulmonary Circulation

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**I**N THE 2 companion papers, we have considered some effects of acute hypoxia on the pulmonary circulation. The present study, concerned with the effects of acute hypercapnia on the pulmonary circulation, was prompted by 2 prospects: (1) that an acute increase in alveolar and arterial  $P_{CO_2}$ , brought about by the inhalation of air enriched with carbon dioxide, might simulate the effects on the pulmonary circulation of the chronic hypercapnia of alveolar hypoventilation, and (2) that regional variations in alveolar ventilation may, through local increments in carbon dioxide tension, change local vascular resistances so as to divert pulmonary arterial blood to better ventilated alveoli.<sup>1</sup>

The effects of inhaling carbon dioxide mixtures on the pulmonary circulation has been investigated by others<sup>1-6</sup> with inconsistent results.

The present report deals with the effects of an acute increase in the carbon dioxide tension ( $P_{CO_2}$ ) of inspired air on pulmonary blood flow and pressures in normal man and in patients with chronic pulmonary emphysema.

## Methods

All tests were performed in the postabsorptive state, without medication. Venous catheterization of the right heart was performed in the usual way and the tip of the catheter was placed in the main pulmonary artery. An indwelling arterial needle was inserted into the right brachial artery. After the catheter and needle were in place, the patient

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was allowed to rest quietly for 10 minutes before observations were begun.

The experimental protocol consisted of either 2 or 3 20-minute breathing periods, separated by 10-minute intervals of rest. During the first and second periods, all subjects but 3 breathed a mixture of 21 per cent oxygen in nitrogen; in these 3 (A.W., B.S., and J.S.) the inspired mixture was 25 per cent oxygen in nitrogen in an attempt to minimize the degree of arterial hypoxemia during the initial periods.

The concentration of carbon dioxide breathed during the final test period was chosen in the following way: in a preliminary trial, a mixture of 5 per cent carbon dioxide in air was administered to each subject; in 7 of them (J.K., P.G., P.M., B.S., L.T., R.R., and J.S.) a "steady state"<sup>7</sup> could not be achieved during preliminary trials during the breathing of 5 per cent carbon dioxide for 15 to 25 minutes, but could be achieved when the 3 per cent carbon dioxide mixture was breathed. In these 7 patients, the 3 per cent carbon dioxide mixture was therefore used on the day of cardiac catheterization.

In each period, pulmonary and brachial arterial pressures were measured at 3-minute intervals. For this purpose, Statham gages were used as pressure transducers, in conjunction with high sensitivity carrier amplifiers and photographic registration of the cathode-ray images. Systolic and diastolic pressures were averaged over at least 2 respiratory cycles, and mean pressures were obtained by planimetric integration.

Between the fifteenth and twentieth minutes of each period, 2 measurements of cardiac output by the direct Fick principle were made. Samples of expired gas and of arterial and mixed venous blood were collected.

The gas samples were analyzed with a Scholander micro-analyzer. Two separate samples were drawn from each gas collection. Duplicate analyses of each sample were required to check within 0.02 volume per cent.

Blood samples were drawn anaerobically. They were immediately analyzed for oxygen content and capacity, and carbon dioxide content by the method of Van Slyke and Neill. The latter data, in conjunction with the arterial blood pH determined by

McInnes-Belcher glass electrode and the line charts of Van Slyke and Sendroy, were used for the calculation of arterial blood carbon dioxide tension.

### Subjects

Seventeen patients were studied. For the sake of presentation, they have been separated into 2 major groups.

The first group contains 5 "control" patients. All had recovered from the acute illnesses that had occasioned their hospitalization. None, except patient H.W., who was found to have asymptomatic essential hypertension, had any evidence of cardiovascular or pulmonary disease. All had stopped taking any medication at least 1 week prior to their first appearance in the laboratory.

The second group consists of 10 patients with chronic pulmonary emphysema; the diagnosis was established, in each instance, in accord with methods previously described from this laboratory.<sup>8</sup> Two patients (B.S. and L.T.) also had silicotuberculosis. Although all of these patients had chronic pulmonary emphysema, there was considerable variation in the amount of disability caused by the disease; in half of the patients, the primary difficulty was respiratory insufficiency; in the remaining half, the disease was complicated by chronic cor pulmonale and carbon dioxide retention. All of the patients with cor pulmonale had had at least 1 episode of heart failure prior to the present study, but none manifested either clinical evidence of heart failure or elevated end-diastolic pressures in the right ventricle at the time of study. Medication in the patients with respiratory insufficiency was confirmed to bronchodilators, whereas the patients with cor pulmonale were restricted to low-salt diets and were receiving maintenance doses of digitalis and diuretics.

The total number of subjects studied is smaller than originally anticipated. This is the result of the 3-stage method that was used to screen candidates for study: (1) only those patients who manifested no intolerance to the usual pulmonary function tests were given preliminary breathing trials with various mixtures of carbon dioxide, (2) only those who manifested no discomfort and satisfied criteria for the "steady state" while breathing 3 or 5 per cent carbon dioxide were subsequently subjected to cardiac catheterization and carbon dioxide breathing, and (3) only those patients who maintained a "steady state" while breathing a carbon dioxide mixture during cardiac catheterization were used for analysis of data.

Of the 22 patients who underwent cardiac catheterization, only 17 satisfied criteria for the "steady state." These criteria corresponded to those previously proposed for experiments with carbon di-

oxide breathing<sup>7</sup> and included (1) values for the respiratory exchange ratio that were virtually identical during successive periods of carbon dioxide breathing and that did not differ appreciably from control values and (2) stable levels of minute ventilation, blood flow, arteriovenous oxygen difference, and arterial blood carbon dioxide tensions during the test as well as the control periods. The criterion of comparable respiratory exchange ratios ( $R_E$ ) during control and test periods is of particular note, since a low value for  $R_E$  during carbon dioxide breathing, a consistent reflection of an "unsteady state," leads to an underestimation of the oxygen uptake and, consequently, of blood flow calculated by the Fick principle.

### Results

Before commenting on the changes in blood pressure and flow induced by breathing carbon dioxide, it is pertinent to analyze the concomitant changes in gas exchange. These are summarized in table 1; the corresponding values for arterial blood gases, pulmonary blood flow and pressure, and systemic arterial blood pressure are listed in table 2.

#### Minute Ventilation, Gas Exchange, and Arterial Blood $P_{CO_2}$

The average resting minute ventilation ( $\dot{V}_E$ ) was similar in the control and emphysema groups, averaging 5.63 and 5.76 liters per minute per square meter of body surface, respectively. During the breathing of the mixtures of carbon dioxide in air, however, the increase in minute ventilation in the control group averaged 153 per cent, whereas the mean increase for the entire emphysema group was only 100 per cent. Despite this difference in ventilatory response, the average increases in arterial blood  $P_{CO_2}$  were similar in the two groups.

The respiratory exchange ratios ( $R_E$ ) were similar in the control and test periods, since  $R_E$  was a prime criterion for the "steady state." Although average values for oxygen uptake were similar in the 2 groups, there was considerable variation in the emphysema group, with the largest increments during carbon dioxide breathing occurring in the patients with advanced pulmonary disease (J.S. and B.S.). These unusual increments in

Table 1  
Changes in Minute Ventilation and Gas Exchange While Breathing CO<sub>2</sub> in Air

Subject	Age yrs.	BSA	Breathing mixture: 21% or 25% O <sub>2</sub> in N <sub>2</sub>			Breathing mixture: 3% or 5% CO <sub>2</sub> in air		
			$\dot{V}_E$ L./ min./M. <sup>2</sup>	$\dot{V}_{O_2}$ ml./ min./M. <sup>2</sup>	R <sub>E</sub>	$\dot{V}_E$ L./ min./M. <sup>2</sup>	$\dot{V}_{O_2}$ ml./ min./M. <sup>2</sup>	R <sub>E</sub>
Control subjects								
J.K.	38	1.87	5.13	152	.85	10.60	193	.87
H.W.	53	1.83	5.86	149	.87	15.20	153	.82
P.B.	40	1.72	6.34	125	.90	15.60	137	.88
D.M.	39	1.71	6.06	141	.80	17.20	147	.71
E.C.	23	1.62	4.74	155	.81	12.70	182	.75
Average			5.63	144	.85	14.26	162	.81
Patients with chronic pulmonary emphysema								
L.T.	37	1.94	3.71	138	.76	7.29	160	.77
G.G.	51	1.58	6.06	141	.83	17.20	147	.75
T.B.	57	1.69	4.58	132	.87	24.70	140	.84
R.R.	58	1.98	5.86	129	.84	8.64	149	.89
P.G.	58	1.47	5.62	125	.89	8.94	154	.91
W.B.	49	1.62	5.80	120	.91	10.65	133	.81
P.M.	52	1.63	7.60	154	.76	9.11	153	.76
A.W.	64	1.49	7.41	149	.78	11.50	149	.72
B.S.	62	1.46	6.38	145	.77	9.30	184	.79
J.S.	63	1.56	4.55	116	.72	8.29	151	.75
Average			5.76	135	.82	11.56	152	.80

oxygen uptake may be related, at least in part, to abnormal increments in the work of breathing.

#### Arterial Blood Oxyhemoglobin Saturation

The arterial blood oxyhemoglobin saturation averaged 97 per cent in the control group; in the emphysema group, the initial oxygen saturations averaged 89 per cent. During CO<sub>2</sub> breathing, the saturation in the control group rose to 100 per cent, whereas in the emphysema group the saturation increased to only 93 per cent.

#### Cardiac Output ( $\dot{Q}$ )

As indicated in table 2, the average cardiac index for the control group while breathing ambient air was 3.44 liters per minute; the corresponding average for the emphysema group was appreciably lower, averaging 2.77 liters per minute. The highest resting flow was measured in patient P.M., who also had the greatest degree of arterial oxyhemoglobin unsaturation (76 per cent). While breathing the carbon dioxide mixtures, the control group manifested a mean increase in cardiac output

of 7 per cent, whereas the emphysema group had an average increase of 16 per cent. The change in blood flow for the individual patients is indicated in table 2. Although the mean increase in cardiac output in both groups was statistically not significant ( $p > .01$ ), 5 of the 15 patients had increases in flow that exceeded 0.48 liter per minute per square meter of body surface; this value had been previously calculated in this laboratory as representing the limit of variation that might, with 95 per cent confidence, be anticipated to occur between successive Fick measurements.<sup>9</sup> These patients (E.C., P.G., W.B., B.S., and J.S.) also had the largest increases in oxygen uptake, ranging from 11 to 30 per cent; indeed, the largest increment in flow of +41 per cent occurred in patient J.S., who showed the largest increment in oxygen uptake (+30 per cent). For the group as a whole, however, a statistically significant correlation between increase in oxygen uptake and increase in flow could not be established ( $r$  not significant at 5 per cent level). The increases in cardiac output were due predominantly to increase in

Table 2

*Changes in Arterial Blood Gases, Cardiac Output and Pulmonary and Systemic Arterial Blood Pressures While Breathing CO<sub>2</sub> in Air*

Subject	Arterial blood Pco <sub>2</sub> O <sub>2</sub> Sat. mm. Hg. %		Breathing mixture: 21% or 25% O <sub>2</sub> in N <sub>2</sub>				Breathing Mixture: 3% or 5% CO <sub>2</sub> in air			
			Cardiac index L./min./ M. <sup>2</sup>	Pulmonary artery pressure s/d, m mm. Hg	Brachial artery pressure s/d, m mm. Hg	Arterial blood Pco <sub>2</sub> O <sub>2</sub> Sat. mm. Hg %	Cardiac index L./min./ M. <sup>2</sup>	Pulmonary artery pressure s/d, m mm. Hg	Brachial artery pressure s/d, m mm. Hg	
Control subjects										
J. K.	40	97	3.70	21/8, 15	120/70, 91	42	99	3.50	18/7, 14	123/73, 95
H. W.	35	98	3.61	23/10, 17	180/103, 138	40	100	3.92	20/7, 13	187/103, 142
P. B.	36	97	3.25	21/8, 13	120/73, 94	44	100	3.52	26/8, 15	152/86, 119
D. M.	35	98	3.25	21/9, 14	122/77, 97	42	100	3.58	23/10, 16	134/81, 105
E. C.	38	96	3.37	14/7, 10	111/71, 88	47	99	3.86	17/9, 13	130/74, 99
Average	37	97	3.44	20/8, 14	131/79, 102	43	100	3.68	21/8, 14	145/83, 112
Patients with chronic pulmonary emphysema										
L. T.	37	91	3.27	34/13, 24	136/82, 105	43	94	3.50	38/14, 27	145/87, 112
G. G.	37	95	2.59	29/17, 22	118/74, 93	43	100	2.97	33/18, 24	139/82, 107
T. B.	38	94	3.07	23/12, 18	150/81, 111	42	98	3.19	29/12, 19	163/84, 116
R. R.	43	93	2.75	27/14, 20	130/81, 104	52	97	2.65	30/15, 21	140/83, 109
P. G.	44	95	2.41	27/15, 20	128/77, 98	51	99	3.22	31/17, 24	149/87, 109
W. B.	45	93	2.30	36/12, 22	145/80, 106	57	96	3.01	43/16, 28	147/94, 121
P. M.	43	76	3.94	56/23, 38	124/69, 92	50	86	3.82	59/26, 39	136/72, 96
A. W.	48	87	2.93	28/15, 22	133/69, 93	58	96	2.90	31/17, 24	150/73, 104
B. S.	51	85	2.17	92/38, 60	123/80, 100	59	80	2.83	108/45, 72	144/92, 117
J. S.	59	83	2.33	66/30, 44	132/72, 96	61	86	3.28	75/32, 51	153/80, 114
Average	45	89	2.77	43/19, 29	132/77, 100	52	93	3.13	48/21, 33	147/84, 110

stroke volume, since changes in heart rate were slight. As can be seen in table 2, there was no consistent relation between change in the arterial blood PCO<sub>2</sub> and the cardiac output; thus, the largest increase in blood flow during carbon dioxide breathing occurred in patient J.S., in association with an increase in arterial blood PCO<sub>2</sub> of 2 mm. Hg and an increase in oxyhemoglobin saturation of 3 per cent. Nor could a consistent relation be established between cardiac output and minute ventilation.

#### Pulmonary Artery Pressure

In the control group, initial pulmonary artery pressures were all normal; in the emphysema group on the other hand, these pressures were distinctly elevated in half the patients, with the highest values occurring in patient B.S. with silicotuberculosis. During carbon dioxide breathing, the average systolic, diastolic, and mean pressures remained unchanged in the control group; by way of contrast, in the emphysema group, pulmonary artery pressures increased from an average of

43/19, with a mean of 29 mm. Hg during the breathing of ambient air to a level of 48/21 with a mean of 33 mm. Hg during carbon dioxide breathing. The increase in mean pulmonary artery pressure during carbon dioxide breathing for the emphysema group was statistically significant ( $p < .01$ ). In only 3 patients (B.S., W.B., and J.S.) were there increases in mean pressure that exceeded 5 mm. Hg; in these 3 patients, the increments in mean pressure were associated with increases in flow ranging from 30 to 40 per cent above control. These changes in the control subjects and the patients are detailed in table 2. In the 10 patients, only a questionable statistical significance could be established between change in pulmonary artery pressure and cardiac output (r significant at 5 per cent level); furthermore, no correlation existed between the change in pulmonary artery pressure and minute ventilation, arterial blood PCO<sub>2</sub>, or arterial blood oxyhemoglobin saturation.

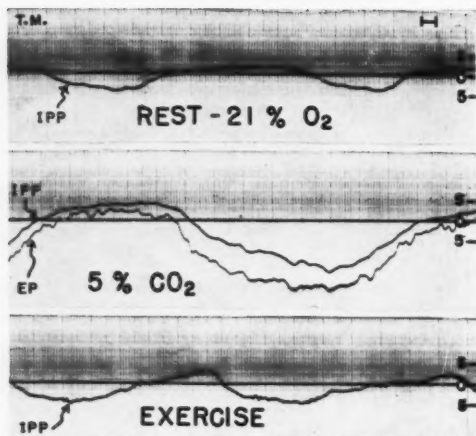


Figure 1

The variations in intrapleural pressures (IPP) and in esophageal pressure (EP) during  $\text{CO}_2$  breathing (5 per cent  $\text{CO}_2$ ) and during exercise. The pressure is expressed in mm. Hg.

To circumvent the limitations inherent in the statistical analysis of data from a heterogeneous group of patients with chronic pulmonary emphysema, individual cases were analyzed in the attempt to uncover the contribution of a change in pulmonary blood flow, in arterial oxygen saturation, or in arterial  $\text{P}_{\text{CO}_2}$  to the pulmonary pressor response. In 6 patients, such a distinction was not possible. On the other hand, evidence from 4 others indicated that the increment in pulmonary arterial pressure stemmed largely from the increment in pulmonary blood flow. Thus, in 3 subjects (P.M., A.W., and R.R.), despite large increases in arterial  $\text{P}_{\text{CO}_2}$ , neither pulmonary arterial pressure nor blood flow changed. On the other hand, in subject J.S., who manifested no increase in arterial  $\text{P}_{\text{CO}_2}$ , an increase in pulmonary blood flow was associated with a large increase in pulmonary arterial pressure.

#### Brachial Artery Pressure

The control systemic blood pressures were normal in all patients except H.W., who had essential systemic hypertension. During carbon dioxide breathing, despite small increments in cardiac output, considerable incre-

ments in systemic blood pressures were measured in the control and patient groups. The increase in systemic blood pressure during carbon dioxide breathing affected primarily the systolic blood pressure; the smallest increase occurred in the systemic hypertensive patient. The changes in mean brachial artery pressure stand in sharp contrast to the slight changes in pulmonary artery pressure.

#### Discussion

The breathing of air enriched with carbon dioxide may conceivably affect the pulmonary circulation in the same way as the breathing of oxygen-poor gas mixtures.<sup>1-5</sup> In contrast to the effects of acute hypoxia, however, acute hypercapnia in the normal subject is not associated with an increase in either pulmonary arterial blood flow or pressure. On the other hand, some patients with chronic pulmonary emphysema do manifest an increase in both pulmonary arterial blood pressure and flow during  $\text{CO}_2$  breathing. In such instances, although the situation is complicated by concomitant changes in the oxygen saturation of arterial blood, the evidence seems clear that an increase in pulmonary arterial pressure is invariably associated with an increase in pulmonary blood flow. This conclusion is in accord with that of Westcott et al.<sup>6</sup>

The possibility exists that the use of a stable atmospheric pressure as a baseline for the measurement of pulmonary arterial pressure may obscure variations in the transmural pulmonary arterial pressure as tidal volumes are increased. That changes in intrapleural pressure (IPP) do occur during  $\text{CO}_2$  breathing is well known. It may be seen in figure 1 that  $\text{CO}_2$  breathing may be associated with wider excursions of intrapleural pressure than obtain during moderate exercise. Nonetheless, despite the augmented swings, the mean intrapleural pressure varies from control by only a few mm. Hg.

The mechanisms responsible for the increase in pulmonary blood flow in some of the emphysematous patients during  $\text{CO}_2$  breathing are not apparent. Three likely prospects are (1) an abnormal work of breathing arising

from the disease of the lungs and airways, (2) an inordinate ventilatory drive acting on a mechanically deficient chest bellows, and (3) some obscure effect of the carbon dioxide on the myocardium. The present study does not distinguish among these possibilities.

Finally, others have suggested on the basis of observations on isolated vascular segments<sup>10</sup> and on special animal preparations<sup>3-5</sup> that the breathing of air enriched with CO<sub>2</sub> may elicit pulmonary vasoconstriction. The present studies afford no indication that these conclusions apply to intact man.

### Summary

The effects of inhaling 5 per cent carbon dioxide in air on the pulmonary arterial blood pressure and flow were studied in 5 subjects with normal pulmonary circulations and in 10 patients with chronic pulmonary emphysema.

In the 5 control subjects, with an average increase in arterial  $P_{CO_2}$  of 6 mm. Hg (37 to 43) and a 3-fold increase in minute ventilation, both pulmonary arterial blood pressure and flow remained unchanged. In the 10 patients with chronic pulmonary emphysema with a similar increase in arterial  $P_{CO_2}$  (45 to 52) and a 2-fold increase in minute ventilation, there was a 14 per cent increase in cardiac output and a rise in pulmonary arterial mean pressure of 4 mm. Hg. In these patients an increment in pulmonary arterial pressure was invariably associated with an appreciable increment in blood flow.

The present study affords no support for the view that the breathing of air enriched with carbon dioxide elicits pulmonary vasoconstriction in either normal subjects or in patients with chronic pulmonary disease.

### Summario in Interlingua

Esseva studiate, in 5 subjectos con normal circulation pulmonar e in 10 patientes con chronic emphysema pulmonar, le effectos exercite per le inhalation de 5 pro cento de bioxydo de carbon in aere super tensione e le fluxo del sanguine pulmono-arterial.

In le 5 subjectos de controlo—in qui il habeva un augmento medie de 6 (ab 37 ad 43) mm de Hg in

le tension de CO<sub>2</sub> arterial e un triplie augmento del ventilation per minuta—tanto le tension como etiam le fluxo del sanguine pulmono-arterial remaneva inalterate. In le 10 patientes con chronic emphysema pulmonar—in qui il habeva un simile augmento in le tension de CO<sub>2</sub> arterial (ab 45 ad 52) e un duplie augmento del ventilation per minuta—le rendimento cardiac montava per 14 pro cento, e le tension pulmono-arterial medie esseva augmentate per 4 mm de Hg. In iste patientes, un augmento del tension pulmono-arterial esseva invariabilemente associate con un appreciable augmento del fluxo de sanguine.

Le presente studio ha producite nulle resultado que supportarea le conception que le inhalation de aere inricchite de bioxydo de carbon evoca un vasoconstriction pulmonar in subjectos normal o in patientes con chronic morbo pulmonar.

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# Intermittent Disappearance of the Murmur of Patent Ductus Arteriosus

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**T**HE MURMUR of patent ductus arteriosus is usually considered to be stable, although it may be modified by certain pharmacologic agents.<sup>1, 2</sup> Absence of the typical ductus murmur has most commonly been ascribed to the presence of relative or absolute pulmonary hypertension;<sup>3, 4-6</sup> occasionally it is ascribed to heart failure,<sup>7</sup> a very small ductus,<sup>1, 8</sup> or spontaneous closure of the ductus.<sup>7, 9, 10</sup>

Spontaneous disappearance and subsequent reappearance of the typical murmur of patent ductus unassociated with pulmonary hypertension, heart failure, polycythemia or other congenital anomalies has not been previously documented to our knowledge. The purpose of this report is to describe this phenomenon and to attempt to explain it.

## Case Report

The patient, a 9-year-old girl, was studied because of a heart murmur. She was born after 7 months' gestation, weighing about 1,700 Gm. A murmur was discovered at age 2 but, according to the mother, it was not always heard. The child had frequent upper respiratory tract infections and was said to tire more easily than other children. There was no history of cyanosis, edema, squatting, fainting, or significant retardation in growth and development.

It became clear that the patient could tell whether or not the thrill accompanying her murmur was present. She stated that her "washing machine" would disappear with quiet rest and return when she became excited.

The patient's immediate family, including 3 younger sisters, were in good health. A younger brother had died within a few days of birth of congenital anomalies of the spinal cord. A ma-

ternal aunt was thought to have had some form of congenital heart disease and had died at age 42.

The patient weighed 54 pounds and was 49 inches tall (both in the fifteenth percentile). She was alert, well developed, slender, and slightly pale. Clubbing, edema, cyanosis, and neck-vein distention were not present. The lungs were clear. The point of maximum impulse was at the midclavicular line in the fifth intercostal space. The second sound in the pulmonic area was palpable, and at times a long thrill could be felt in the pulmonic area. The pulmonic second sound was louder than the aortic second sound. In the pulmonic area and for some distance about it could be heard a continuous murmur with a rough systolic component of maximum intensity at the time of the second sound and continuing through diastole as a softer, higher pitched murmur. The peripheral pulses were bounding and cuff blood pressure in the left arm was 107/52.

During several examinations the murmur abruptly disappeared for varying lengths of time (fig. 1). This usually occurred during quiet rest or sleep. When the bruit was inaudible, cuff blood pressures averaged 101/75. After periods of time, as long as 30 minutes, the murmur and thrill returned.

Tests of blood and urine and an electrocardiogram were normal. X-rays of the chest demonstrated minimal prominence of the pulmonary artery segment, but otherwise the cardiac contour and lung fields were unremarkable. At fluoroscopy the heart appeared hyperdynamic. Along the right border of the heart there appeared to be intrinsic expansile pulsations of the pulmonary vessels. The left ventricle did not completely clear the spine on deep inspiration in the left anterior oblique position.

The patient was studied on many occasions. Right heart catheterization was carried out under intravenous Pentothal anesthesia. Pressures were obtained with an electromanometer and recorded on a multichannel direct-writing apparatus. Blood oxygen determinations were made according to the method of Van Slyke and Neill.<sup>11</sup> Duplicate determinations agreed to within 0.2 to 0.3 volumes per cent. Phonocardiograms were recorded in the log position on a Sanborn Twin-Beam Cardiette. Determinations of arterial PCO<sub>2</sub>, expired PCO<sub>2</sub>,

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The opinions or assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Department of the Navy or of the naval service at large.

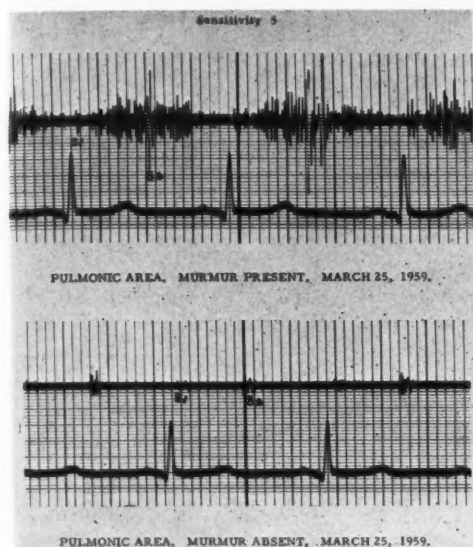


Figure 1

Top. Typical continuous murmur usually heard in this patient. Bottom. Recording in same area at same sensitivity demonstrating spontaneous disappearance of the murmur.

and tidal volume were performed in order to calculate physiologic dead space from the Bohr equation.

At thoracotomy a patent ductus arteriosus was found, divided, and sutured without difficulty. The patient recovered without incident and 2 months later she was reported to be less easily fatigued and eating unusually well.

### Observations

#### Cardiac Catheterization

Data obtained at right heart catheterization were consistent with the clinical diagnosis of patent ductus arteriosus (table 1). Before the procedure was begun, the murmur was inaudible. The murmur returned as the procedure started and remained throughout the study. A significant oxygen rise occurred at the pulmonary artery level and the pulmonary blood flow was more than twice systemic blood flow. Pressures in the pulmonary artery and right ventricle, as well as the calculated pulmonary vascular resistance, were well within the range of normal. Brachial artery pressure was normal.

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Table 1

Data from Right Heart Catheterization. Murmur Was Present during the Procedure

Location	Pressures in mm. Hg		Oxygen content volumes per cent*	Per cent oxygen saturation
	S/D	Mean		
Superior vena cava	5/0	3	10.2	73
Right atrium	6/3	4	9.7	69
Right ventricle	21/2-6	12	9.6	69
Main pulmonary artery	21/13	16	12.9	92
Right pulmonary artery	20/13	16	12.0	86
Pulmonary "capillary"	15/5	10	—	—
Left brachial artery	118/73	90	13.8	99

Systemic flow ( $O_2$  consumption assumed to be 160 ml./min./ $M^2$ ) = 3.5 L./min.

Pulmonary flow (with use of RPA  $O_2$  content) = 7.9 L./min.

Pulmonary vascular resistance = 138 dynes/sec./cm.<sup>-2</sup>

\*Oxygen capacity of blood = 14.0 volumes per cent.

#### Phonocardiographic Studies

Repeated attempts were made to demonstrate a particular posture or other state that was consistently associated with disappearance of the murmur. On one occasion it was found to be absent while the patient was standing, but generally it disappeared with the patient quietly resting or sleeping in the supine position. Assumption of the latter attitude, however, was not invariably followed by disappearance of the bruit. Knee-chest, prone, Trendelenburg, Fowler, 60-degree upright tilt, and various lateral positions did not affect the murmur.

The murmur was observed to disappear either abruptly or gradually. When the disappearance was gradual, the diastolic portion would shorten and disappear, then the systolic component would progressively diminish in intensity until it became inaudible. For periods varying up to 30 minutes normal heart tones only would be heard. Reappearance was also gradual or abrupt (fig. 2). Marked respiratory variations in the murmur were sometimes noted upon its return, i.e.,

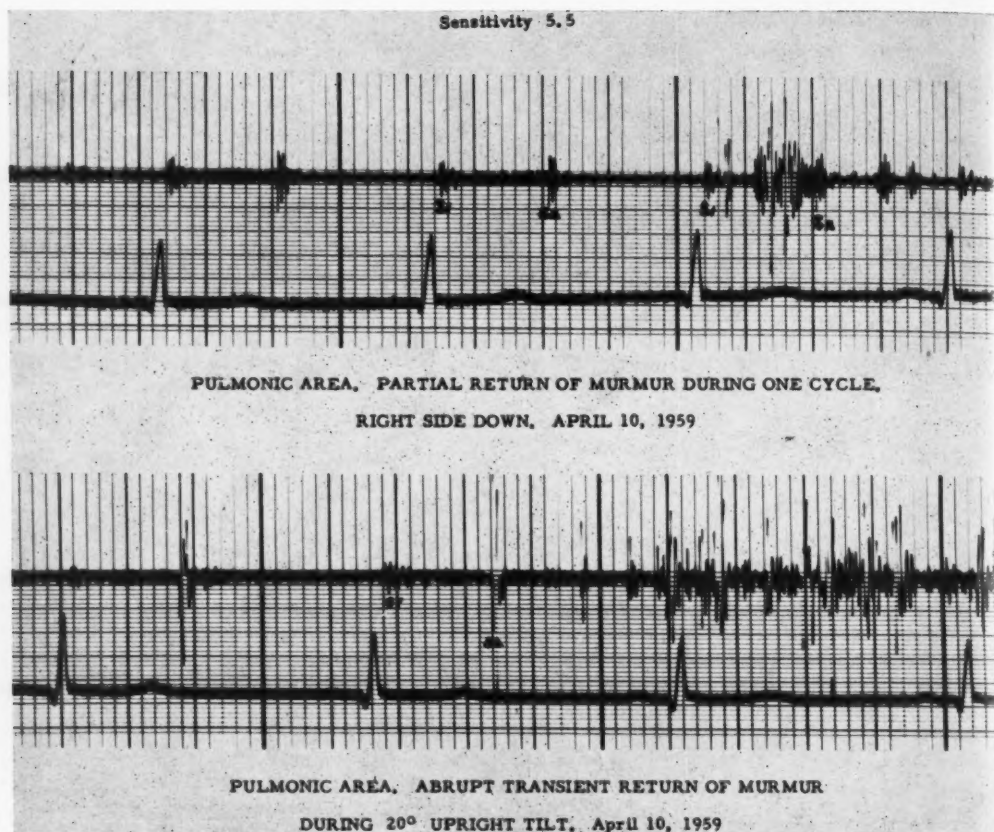


Figure 2

Top. Inaudible, low-pitched vibrations are present in systole. The murmur partially returns during one cycle. Bottom. Abrupt return of the murmur; it disappeared again after several cycles.

a loud continuous murmur in expiration, near absence to absence during inspiration followed by re-establishment and no noticeable changes throughout the respiratory cycle. A thrill was present when the murmur was most pronounced; when the murmur was soft or absent, no thrill was palpable.

The effects of various agents were tested. No agent produced complete disappearance like what occurred spontaneously. Anxiety (increased cardiac output, heart rate, and stroke volume)<sup>12</sup> induced by impending and actual needle pricks (to administer local anesthesia for arterial puncture) made the murmur louder. Inhalation of 100 per cent

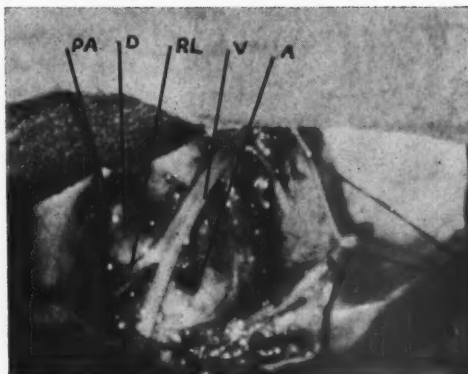
oxygen (decreased pulmonary vascular pressure)<sup>2, 13, 14</sup> and carotid sinus massage produced no consistent change in the murmur. Inhalation of 13 per cent oxygen for 5 minutes (increased pulmonary vascular pressure)<sup>2</sup> brought out marked respiratory variations in the bruit. These were manifest as striking diminutions in amplitude during inspiration. Amyl nitrite inhalations (systemic vasodilatation)<sup>15</sup> produced a decrease in amplitude and shortening of the diastolic portion of the murmur at the onset of the facial flush on one occasion. On a second occasion amyl nitrite transiently produced the same effect at the height of the flush.

That the murmur itself might have been an unusually loud venous hum was ruled out by the complete lack of effect of movements of the head and unilateral or bilateral jugular venous compression.

Arm blood pressures were repeatedly determined with a pediatric sphygmomanometer. The mean of 8 determinations on several occasions when the murmur was absent was 101/75 (range 98-105/64-80, mean pulse pressure of 26). The mean of 5 determinations when the murmur was present was 107/52 (range 100-110/44-65, mean pulse pressure of 55). Despite its limitations as compared with direct intra-arterial pressure recordings, repeated external cuff pressures have value since they were obtained by a single observer. The narrowed pulse pressure, largely due to an increase in diastolic pressure, observed when the murmur was absent, suggested that the shunt through the patent ductus arteriosus might have diminished greatly at these times.

#### Physiologic Dead Space Studies

In 1959, Riley et al.<sup>16</sup> reported that assumption of the upright position in normal subjects resulted in an increase in physiologic dead space due to lack of perfusion of alveoli in the upper parts of the lungs because of inadequate pressure head in the pulmonary artery. In an attempt to correlate the presence or absence of the ductus murmur with the presence or absence of shunt flow, it was reasoned that when a large volume of arterial blood was shunted into the pulmonary circulation, there might be more complete perfusion of alveoli in the top of the lung in the upright position. Therefore, the increase in physiologic dead space on assuming this position would not be so marked as might be expected in normal subjects. In this patient,  $\frac{\text{Physiologic dead space}}{\text{Tidal volume}} \times 100$  increased from 23 per cent in the supine position to 30 per cent in the standing position while the murmur was audible, and from 22 per cent to 49 per cent while the murmur was absent. Although this procedure is probably not sensitive enough to be a practical test for detection



**Figure 3**

*Photograph taken at surgery in the present case. Note the rather curved course of the ductus. PA, pulmonary artery; D, ductus arteriosus; RL, recurrent laryngeal nerve; V, vagus nerve; A, aorta.*

of shunts, the results were thought suggestive of an intermittent decrease in pulmonary blood flow associated with the intermittent absence of the ductus murmur.

#### Observations During Surgery

When the chest was open and the mediastinal structures were exposed, a thrill was felt over the ductus arteriosus and the adjacent portion of the left pulmonary artery. Inadvertent rapid infusion of 1 liter of 5 per cent dextrose in water produced no palpable effect on the thrill or on the vital signs. The ductus was about 1 cm. in outside diameter and 1.5 cm. long. It arched superiorly from the aorta and angulated somewhat inferiorly as it entered the pulmonary artery (fig. 3). No unusual nerve to the ductus was found, and mechanical irritation from dissection of adherent structures caused no change in diameter or in the thrill. Slight dorsal displacement of the pulmonary artery by the operator's finger abolished the thrill. This appeared to result from angulation of the ductus so as to close its lumen at the point of curvature several millimeters from its junction with the pulmonary artery.

The patient was not placed in the supine position during surgery. The amount of traction required to abolish the thrill was very slight.

### Discussion

The phenomenon of spontaneous intermittent complete disappearance of the typical murmur of patent ductus arteriosus may, in an individual patient, lead to difficulty in arriving at the proper diagnosis.<sup>17</sup> This was apparently true during the earlier years of life in our case. Maneuvers designed to increase cardiac output or elevate systemic pressures might be helpful in bringing out the murmur when it is absent.<sup>1</sup>

In attempting to explain the striking changes in the murmur one is struck by the evidence for intermittency of shunt flow, namely: (1) widened pulse pressure when the murmur was present with distinctly narrower, normal pulse pressures in its absence; (2) physiologic dead space changes suggestive of abnormally increased perfusion of the pulmonary vascular bed when the murmur was audible in contrast to the normal postural changes in its absence; (3) ready abolition of the thrill over the ductus and adjacent left pulmonary artery when gentle dorsal traction was applied to the pulmonary artery. None of the pharmacologic agents made the murmur disappear. Inhalation of a low oxygen mixture resulted in respiratory variations in the murmur rather similar to those occasionally observed during its spontaneous reappearance. This decrease in amplitude with inspiration and increase during expiration of the machinery murmur has been noted in occasional patients with patent ductus arteriosus<sup>18</sup> as well as by Dawes et al. in some of their spontaneously breathing newborn lambs.<sup>20</sup> No hemodynamic data were recorded when these effects were manifest in the present case. It might be suggested, however, that the respiratory variations following the breathing of a low oxygen mixture might have resulted from changes in the aorta to pulmonary artery pressure gradient due to an increase in pulmonary vascular pressure and decreased left ventricular output during inspiration.<sup>21</sup> When these variations occurred spontaneously, inspiratory reductions in left ventricular output alone may have been responsible. The slight reductions in amplitude after amyl ni-

trite might be explained by mild reductions in flow rate produced by any pressure gradient changes during generalized systemic vasodilatation.

Levine and Harvey stated "in some cases the continuous murmur is intermittent, and its presence and disappearance suggest a fluctuation of the level of pulmonary hypertension."<sup>19</sup> This is considered unlikely in the present instance, for even in the case of primary pulmonary hypertension reported by Gorlin et al.,<sup>22</sup> in which acute pulmonary vasoconstriction apparently occurred, the increase in mean pulmonary artery pressure was about 20 mm. Hg. This amount of increase would bring our patient's mean pulmonary artery pressure to less than half her arterial mean pressure, a level probably not high enough to change greatly an established continuous murmur.

Other causes of atypical or absent murmurs such as the presence of associated defects,<sup>23</sup> polycythemia, congestive heart failure<sup>7</sup> appear to have been adequately eliminated.

The cause of the apparent occasional cessation or marked diminution of shunt flow and absence of the murmur in this patient would appear to be mechanical rather than physiologic. In this case acute angulation of the ductus with obliteration of the lumen could have occurred if slight shifts in mediastinal structures can be presumed to have taken place in the intact individual. Quiet rest, particularly in the supine position, might have allowed such shifts to have taken place.

### Summary

Transient spontaneous disappearance of the machinery murmur in an otherwise typical case of patent ductus arteriosus unassociated with pulmonary hypertension is described.

Observations of blood pressure changes, physiologic dead space variations in the upright and horizontal postures, and the anatomy of the ductus arteriosus suggested that shunt flow was absent or markedly reduced during the periods in which the murmur was inaudible.

### Acknowledgment

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### Summario in Interlingua

Es describe le transiente e spontanee disparition del murmure de locomotiva in un alteremente typic caso de patente ducto arteriose sin association con le hypertension pulmonar.

Observationes de alterationes in le tension del sanguine, de variationes del spatio morte physiologic in postura erecte e horizontal, e le anatomia del ducto arteriose suggereva que shunting de fluxu sanguinee esseva absente o marcatamente reduceite durante le intervallos quando le murmure esseva inaudibile.

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# Liver Function in Patients with Elevated Serum Cholesterol or Low-Density Lipoproteins

By H. ENGELBERG, M.D.

**A**N UNDERSTANDING of the normal mechanism involved in the removal of alimentary fat from the bloodstream is important physiologically and also clinically since the demonstration of delayed clearance of alimentary lipemia in atherosclerotic patients.<sup>1-7</sup> Most fat absorbed from the bowel enters the blood via the thoracic duct lymph, chiefly in the form of chylomicra and lipomicros, which are particles composed predominantly of triglycerides and small amounts of cholesterol, phospholipid, and protein. Normally the particles are rapidly removed from the circulation.<sup>8-11</sup> Since the systemic capillary wall is relatively impermeable to lipids,<sup>12-14</sup> and particularly to the larger chylomicra,<sup>15, 16</sup> various pathways for the transfer of alimentary neutral fat from the blood to the tissues must be considered other than direct diffusion through the capillary wall to the extravascular fluid. Three possible mechanisms have been proposed: triglyceride lipolysis by a heparin-activated enzyme (lipoprotein lipase) taking place in the plasma or at the capillary endothelial wall, phagocytosis of chylomicra by reticuloendothelial cells, and finally direct passage of chylomicra as such from the plasma into the liver. This latter possibility is supported by observations of fat within the liver parenchymal cells shortly after the injection of chyle in experimental animals,<sup>17, 18</sup> and by the demonstration that the endothelium of the hepatic sinusoids is more permeable to chylomicra than is the systemic capillary endothelium.<sup>18</sup> It therefore seemed pertinent to investigate liver function in patients with elevated levels of

serum cholesterol or of low-density lipoproteins. A survey of the literature revealed no systematic study of this question although liver function tests have undoubtedly been performed in many such patients.

## Methods

The individuals selected for this study were private patients in whom elevated levels of serum cholesterol and low-density lipoproteins had been found on at least 2 separate occasions. In a few cases only one of the lipids was abnormal. Serum cholesterol was measured by one of the standard methods,<sup>19</sup> and the lipoproteins were determined by ultracentrifugal analysis.\* Although the "normal" values for these lipoproteins have not been defined, the range of means for standard Sf 0-12 lipoproteins in men aged 30 to 69 is 367 to 407 mg. per cent, and in women is 301 to 392 mg. per cent. The means for the Sf 12 to 400 class of lipoproteins in men is 217 to 235 mg. per cent, and in women 142 to 274 mg. per cent.<sup>20</sup> The liver function tests used were the thymol turbidity, cephalin flocculation, sulfobromophthalein excretion, cholesterol esterification and, although not shown in the table, the urine urobilinogen excretion, all performed according to standard procedures. Forty-two patients were studied but cholesterol esters and urine urobilinogen were not measured in all cases.

## Results

The findings are shown in table 1. There were 34 men and 8 women, ranging from 36 to 69 years in age. Four of the patients had diabetes and 2 were alcoholic. Approximately half of the remainder were clinically normal, and the rest had coronary atherosclerotic disease. The tests were normal in most instances. The sulfobromophthalein test was definitely abnormal in 3 persons, the 2 alcoholic ones and subject J. G., who had an 11.5 per cent retention. In 5 others the values were very slightly elevated, 8 to 9.1 mg. per

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\*These analyses were performed at the Institute of Medical Physics, Belmont, Calif.

Table 1  
Serum Cholesterol and Lipoproteins, and Liver Function Tests in Forty-two Patients

Pt.	Age	Sex	Chol.	Low-density lipoprotein*		Liver function tests				Remarks
				Sf 0-12	Sf 12-400	TT†	CCF‡	BSP§	Chol. ester	
E.M.	64	M	249	575	521	0	0	2		
S.G.	52	F	422	437	565	4	+	2		
S.E.	37	F	420	804	82	2	0	.6	320	
S.K.	44	M	336	530	619	3	0	1.2		
B.K.	55	M	283	353	825	2	0	3.5	195	
L.M.	47	M	306	559	500	0	0	1.0	210	
B.R.	41	M	306	626	370	1	0	0		
T.B.	40	M	198	302	729	4	0	3.1	144	
N.R.	53	M	293	496	624	4	+	3.1		
D.S.	51	M	249	385	465	1	0	1.6		
H.B.	57	M	841	958	654	1	0	8	446	
S.B.	50	M	481	772	1009	1	0	.5	302	
L.D.	44	M	651	799	363	3	0	18	256	Alcoholic
J.G.	47	M	365	617	641	2	0	11.5		
D.T.	43	M	449	898	308	0	0	0	336	
T.C.	47	M	370	588	269	2	0	3.5		
C.L.	49	M	321	473	518	.5	0	2.5		
V.E.	36	M	361	577	482	3	+	23	312	Alcoholic
L.K.	48	M	348	482	941	1	0	1	242	
S.R.	43	M	320	636	362	2	0	3.8		
E.L.	59	F	532	788	879	4	+	1.9	308	
E.G.	50	M	361	688	417	2	0	8.1		
B.C.	46	M	227	391	454	2	0	8		
D.B.	49	M	244	320	489	3	0	3.6	170	
D.B.	51	M	332	730	351	1	0	5.4		
R.G.	59	F	1065	1259	331	2	0	2.7		
A.G.	69	M	336	551	366	3	+	0		
K.L.	63	F	492	847	325	1	0	4.3		
S.H.	68	F	316	716	337	1	0	4.3	221	
L.B.	49	M	324	468	421	3	0	4.3		
F.M.	58	M	270	493	474	2	0	6.4		
J.M.	59	M	336	546	559	3	+	0	236	
K.M.	59	F	265	695	520	1	0	1.6		
A.D.	41	M	697	1111	281	4	0	8.1		
H.B.	39	M	270	513	301	3	+	4.8	187	
E.S.	53	M	340	355	627	2	—	9.1	216	
B.S.	43	M	247	503	335	1	0	3.8		
G.S.	38	M	299	485	287	2	0	0		
B.W.	55	M	256	397	573	4	0	2.2		Diabetic
E.L.	51	M	325	690	245	2	+	2.7		Diabetic
M.G.	57	M	344	512	335	1	+	1		Diabetic
G.E.	64	F	332	402	654	1	0	.5	240	Diabetic

\*Ultracentrifugally analyzed at the Institute for Medical Physics, Belmont, Calif.

†TT, thymol turbidity. Normal range 0 to 4 units.

‡CCF, cephalin flocculation. Normal range 48 hrs. Zero to one plus.

§BSP, bromsulphalein retention. Normal range 0 to 7 per cent.

ent, the significance of which is questionable. These minimal elevations may be secondary to prolonged hyperlipidemia with resultant saturation of the reticuloendothelial system.<sup>21</sup> Urine urobilinogen excretion was normal in

all patients in whom it was measured. The results may be summarized as indicating normal liver function, as it is usually evaluated, in most patients with elevated serum lipid values.

### Discussion

The liver plays a fundamental role in various aspects of fat metabolism, and liver dysfunction may profoundly affect serum lipid values.<sup>22</sup> The data obtained in the present study, however, imply that the liver is not responsible for impairment in the removal of alimentary fat from the bloodstream. Chronically elevated blood lipids, as found in the 42 patients of this study, are usually associated with an impaired clearance of alimentary lipemia.<sup>1-7</sup> It may be argued, however, that none of the tests used directly assessed the ability of the liver parenchymal cells to remove chylomicra. It is therefore pertinent to evaluate other studies of this subject.

Although the systemic capillary wall bars the passage of large lipid-containing molecules from the blood to the tissues,<sup>12-16</sup> the hepatic sinusoids are more freely permeable to chylomicra,<sup>17, 18</sup> at least in experimental animals. Thus hepatic tissue apparently does come into direct contact with triglyceride-laden particles from the blood plasma. It does not necessarily follow that the bulk of this material is removed by the liver; it simply may be altered, perhaps converted to lipoproteins, so as to be soluble in blood. (It has been pointed out<sup>23</sup> that "hepatic lymph is limpid, resembling serum in composition. If, therefore, the liver picks up particulate lipids from the blood it converts them to lipoproteins.") There is also direct evidence on this question. Counts of chylomicra in the hepatic lymph of cats, both fasting and during digestion, were slightly less than counts in plasma,<sup>18</sup> indicating little retention of chylomicra in the liver. Furthermore, liver lymph in normal animals absorbing fat was always clear despite its high chylomicon content, suggesting increased solubility of these particles. In any event, since the liver does not contain a true lipase,<sup>24, 25</sup> and since it inactivates lipoprotein lipase,<sup>26</sup> breakdown of triglyceride by this organ seems unlikely.

Recently the question of the direct uptake of chylomicra by the liver has been approached by 2 groups of investigators using the isolated rat liver. In one study<sup>27</sup> the up-

take of radioactivity by the liver was determined following the perfusion via the portal vein of rat chyle labeled radioactively in the fatty acid moiety. Fifty-four to 60 per cent of the label was taken up by the liver in 3 hours. When the perfusate also contained post-heparin lipoprotein lipase, 75 to 93 per cent of the labeled material was removed, whereas 45 to 55 per cent was removed when the perfusate contained Triton WR 1339, an inhibitor of the lipemia-clearing factor. Liver sections made after 3 hours of perfusion revealed fat globules in the parenchymal cells at the cell margin adjacent to the hepatic sinusoids and only a few fat droplets in Kupffer cells. The authors stated that there was no evidence that Kupffer cells have an essential part in the process of chylomicon uptake, but that their results showed that the liver parenchymal cells can take up chyle fat directly and that an intravascular clearing reaction is not an essential step in the process. Other considerations, however, cast serious doubts upon these interpretations. The flow of lipids from the liver was not measured; therefore the uptake of radioactively labeled fatty acid by the liver simply may indicate exchange between the triglycerides or fatty acid moiety of the chylomicra and similar constituents of the liver cell rather than uptake of chylomicra. The fatty acids of chylomicra have recently been shown to exchange (without preliminary hydrolysis) at the same rate as cholesterol.<sup>28</sup> Furthermore, although Triton markedly slowed the removal of chylomicra from the blood in intact rats,<sup>10</sup> it had no effect on the uptake of fat by the liver *in vitro*. This inconsistency was noted but not explained by the authors. It would seem that the *in vitro* and *in vivo* experiments were not directly comparable. This suggestion is reinforced by the frequent finding of dilated sinusoids and edema and distention of the portal tracts at the end of the perfusion period.

Another study<sup>28</sup> has afforded evidence that the liver has only a minor role, if any, in chylomicon removal. When C<sup>14</sup>-labeled albumin-palmitic acid complex was perfused

through the isolated rat liver, 34 to 43 per cent of the  $C^{14}$  was removed in a single pass-are through the liver, whereas only 4 to 5 per cent was removed when chylomicra-containing palmitate- $1-C^{14}$  was perfused. Again, even the latter figure does not prove that chylomicra are removed, since it may simply represent exchange of the fatty acid moiety. Furthermore, since heparin was used during the operative procedure, the resultant lipoprotein lipase activity may not have been completely removed by the preliminary 1-minute wash of the liver prior to the chylomicron perfusion. This suggestion is supported by the slower disappearance of cholesterol- $4-C^{14}$  from perfused chylomicra than of palmitate- $1-C^{14}$ . This finding is not indicative of liver removal of whole chylomicra but rather of preliminary lipolysis and take-up of the released fatty acid. Thus, it appears most likely that the role of the liver parenchyma is not the removal and lipolysis of chylomicra but their conversion to lipoproteins and subsequent return to the circulation. In fact, an increased rate of clearing of lipemia has been found after the injection of an oil emulsion (Lipomul) intravenously in patients with advanced hepatic damage,<sup>29</sup> an observation inconsistent with the concept of a major primary role of the liver in fat clearing.

We may now consider the evidence that the reticuloendothelial system functions in the clearing of alimentary fat from the blood in man. Much work has been done on this subject in experimental animals, and the results are somewhat confusing. Blockade of the reticuloendothelial system in rats, rabbits, and dogs fed fat and cholesterol resulted in more marked chylomicronemia and hypercholesteremia than in control animals.<sup>30, 31</sup> A decreased rate of clearance of cholesterol from the blood was found when reticuloendothelial cells were partially blocked by carbon.<sup>32</sup> Furthermore labeled cholesterol was found in hepatic Kupffer and parenchymal cells after animals were fed labeled cholesterol and olive oil.<sup>33</sup> However, the fast exchange of the free cholesterol of chylomicra with that of the

high-density lipoproteins,<sup>34</sup> and the rapid equilibration of free cholesterol among plasma, liver, and blood cells<sup>35</sup> short circuited the actual removal of chylomicra, and some exogenous cholesterol was quickly mixed with the endogenous pool. This makes it most difficult to evaluate studies<sup>33</sup> of the immediate fate of newly absorbed labeled cholesterol. Furthermore, other workers have not found that reticuloendothelial-system blockade increased plasma cholesterol levels.<sup>36</sup> Recently, with a magnetic technic for the separation of hepatic parenchymal and Kupffer cells, the phospholipid and neutral fat content of the 2 types of cells was found to be about the same in fasted dogs and rats but the cholesterol content of the Kupffer cells was 2 to 3 times that of the parenchymal cells.<sup>37</sup> These data suggest a specialized role of the reticuloendothelial cells in cholesterol metabolism, but not necessarily a specific role of these cells in the uptake of exogenously administered cholesterol. With the same technic in fat-fed dogs data were obtained that "did not support the concept of a major role of the reticulo-endothelial system in the removal of chylomicra."<sup>38</sup> Direct evidence against chylomicron phagocytosis by reticuloendothelial cells was found after liver perfusion *in vitro*,<sup>27</sup> and after infusions of chyle in intact rats and dogs. In these animals chyle fat never appeared in the Kupffer cells although it did after the injection of oil emulsions.<sup>17</sup> The latter apparently are treated as a foreign substance and cannot be equated with chyle fat. Even with oil emulsions, however, when the reticuloendothelial system was blocked and no fat was found in these cells, the emulsion was removed from the bloodstream at a normal rate, providing additional evidence of the minimal role played by the reticuloendothelial system in the clearance of fat particles.<sup>39</sup>

The discussion thus far leads to the probability that neither the liver nor the reticuloendothelial system occupies the central position in the major physiologic mechanism responsible for the removal of alimentary neutral fat from the bloodstream. They are

involved in this process, and their dysfunction may affect triglyceride metabolism adversely, but the bulk of the available evidence does not suggest that such dysfunction usually accounts for hypertriglyceridemia. We may now turn to a consideration of the remaining pathway proposed for the clearing of alimentary lipemia, the enzymatic heparin lipoprotein-lipase mechanism, reviewed elsewhere.<sup>40</sup> Briefly, following the injection of heparin in animals and man, an active factor can be demonstrated in plasma which catalyzes the lipolysis of the triglyceride component of chylomicra and of the larger low-density or beta lipoproteins. Albumin is essential as the carrier of the released unesterified fatty acids. This lipolytic factor has been identified, without the prior injection of heparin, in animal tissue<sup>41</sup> and in the plasma of some human subjects.<sup>42, 43</sup>

Some clinical observations, insufficiently emphasized heretofore, support the thesis that the heparin lipoprotein-lipase mechanism is probably the major physiologic channel for the removal of alimentary lipemia in man. No defect is known in reticuloendothelial or liver function in the majority of patients with the nephrotic syndrome or with essential hyperlipemia. These individuals, however, do have an interference, of one type or another, with the heparin lipolytic mechanism, and they have a persistent marked elevation of plasma neutral fats and a delayed fat clearance from the blood.<sup>44</sup> In nephrosis there is a lack of circulating albumin, which functions as a carrier molecule for unesterified fatty acids. Studies by various investigators have shown that in this disease, in man and animals, the only demonstrable defect responsible for the increased serum lipids is a lack of the acceptor protein, albumin.<sup>45-48</sup> When plasma albumin rises, lipid levels decrease.<sup>46, 49</sup> In many case reports of essential hyperlipemia no primary liver disturbance has been observed by liver function tests, at surgery, or at autopsy. Several types of abnormalities have been described, however, that markedly hamper the lipoprotein-lipase system. The chylomicra of 1 patient were a very poor sub-

strate for this enzyme.<sup>50</sup> In 3 siblings with the disease, very little lipoprotein-lipase activity appeared following the injection of heparin, indicating a deficiency of the tissue apoenzyme of lipoprotein lipase.<sup>51</sup> In other patients with essential hyperlipemia an inhibitor of post-heparin lipemia-clearing activity has been demonstrated.<sup>51</sup> One other study afforded strong evidence of the physiologic relationship between the heparin lipemia-clearing mechanism and serum low-density lipoproteins with a high neutral fat content. In a survey of 482 patients endogenous plasma-clearing activity was found in 112 individuals.<sup>53</sup> The lipoproteins were determined in 72 of the 112, and in 162 of the subjects in whom clearing activity was not present. In the latter group the Sf 12 to 400 lipoproteins averaged 257 mg. per cent in contrast with 195 mg. per cent in the patients with clearing factor. This difference was statistically significant. These observations and many others recently summarized<sup>54</sup> demonstrate that when the heparin lipolytic enzyme system is impaired, clearance of alimentary lipemia is delayed and serum triglycerides are markedly elevated. This indicates the central role of this mechanism in fat transport. Other pathways for the removal of alimentary fat from the blood undoubtedly exist but they would appear to be subsidiary, and usually are not fully compensatory unless fat intake is reduced substantially.

### Summary

Liver function tests were performed in 42 individuals with increased levels of serum cholesterol and low-density lipoproteins. The tests were normal in 39 patients; the sulfobromophthalein excretion was impaired in 3. These results indicate that disturbances in liver function are not usually involved in elevations of serum triglycerides. Other clinical evidence is discussed which suggests that the heparin lipoprotein-lipase lipolytic mechanism, but not the liver or reticuloendothelial system, occupies the initial role in the removal of alimentary fat from the bloodstream in man.

### Acknowledgment

The technical assistance of Miss Dona Rodensky is gratefully acknowledged.

### Summario in Interlingua

Tests del function hepatic esseva executate in 42 subjectos con augmentate nivellos seral de cholesterol e le lipoproteina a basse densitate. Le tests esseva normal in 39 casos. In 3, le excretion de sulfobromophthaleina esseva disturbate. Iste resultato indica que dysfunction hepatic non es usualmente associate con elevate nivellos seral de triglyceridos. Es discutite altere factos que suggere que le mecanismo lipolytic de heparina, a lipase de lipoproteina, e non le hepate o le systema reticuloendothelial, joca le rolo central in le elimination de grassia alimentari ab le circulation del sanguine in humanos.

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# Occupational Physical Activity and the Degree of Coronary Atherosclerosis in "Normal" Men

## A Postmortem Study

By DAVID M. SPAIN, M.D., AND VICTORIA A. BRADESS, M.D.

THERE is currently considerable speculation concerning the relationship of physical activity to the development of coronary atherosclerosis and ischemic heart disease. Information on this problem has been obtained by animal experimentation, epidemiologic studies on various populations, and clinical investigation of selected patient groups. It has involved studies on the influence of physical activity and "emotional stress" on blood lipids and on the intravascular clotting mechanisms, on the degree of experimentally induced atherosclerosis in animals, and on the relationship of various types of occupations to the morbidity and mortality from coronary "occlusion." Among the reports on the relationship of the different degrees of occupational physical activity to the morbidity and mortality from coronary artery disease are those of Morris et al. in England,<sup>1</sup> Biorek et al. in Sweden,<sup>2</sup> and Spain and Bradess in Westchester County.<sup>3</sup> In all these studies that are based on either mortality records, clinical findings, or postmortem examinations, a positive association was noted between the frequency of ischemic heart disease and the more sedentary types of occupation. This presumptive association has raised several questions. Foremost is the question concerning the phase of coronary artery disease with which sedentary physical activity may be associated. Is the influence of a sedentary life, if any, related to the developmental phase of coronary atherosclerosis (the atherogenic process) or with the

precipitation of acute episodes of ischemic heart disease in individuals with advanced coronary atherosclerosis? In a preliminary study, it was noted that apparently healthy white men between the ages of 30 and 60, who had died suddenly as a result of various accidents, showed no differences, at various corresponding age levels, in the degree of atherosclerosis as related to occupational physical activity.<sup>4</sup> This report is based upon a continuation of this preliminary study in which more significant numbers of individuals have been evaluated in an attempt to determine the presence or absence of such associations.

### Material and Method

Determinations of the degree of coronary atherosclerosis were made on coded hearts from consecutive postmortem examinations on otherwise "normal" white men between the ages of 30 and 60 who had died suddenly and unexpectedly from accident, homicide, or suicide. These cases were studied in the Medical Examiner's Office of Westchester County, New York. This office processes every fatality in the county which results from homicide, suicide, or accident. The approximate population of this county, according to the national 1957 census figure, was 750,000. The county consists of representative suburban areas, moderate-sized cities, towns, and villages. Considerable industry is present, as well as farm areas. Many of the individuals commute daily to work in New York City. The population is stable and, with few exceptions, the autopsied individuals were established residents of this county.

At the end of each postmortem examination the hearts were tagged with a code number and fixed in formalin. The same examiners evaluated the degree of coronary atherosclerosis in the entire study. All estimates of the degree of coronary atherosclerosis were made without any prior knowledge of the age and occupation of the individuals whose particular hearts were being examined. All major branches of the coronary arteries were examined in cross-section at intervals of 3 mm. The degree

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Table 1

*Degree of Coronary Atherosclerosis in Sudden Fatalities from Accident, Suicide, and Homicide (Sedentary Occupations)*

Age	Number of cases				Index*
	Degree of Atherosclerosis				
	±	+	++	+++	
31—35	8	5	2	0	0.9
36—40	2	4	4	1	1.36
41—45	2	5	8	1	1.50
46—50	1	5	8	4	1.82
51—55	0	3	6	9	2.33
56—60	0	4	13	7	2.12
Total	13	26	39	22	

\*Index figures are the average degree of coronary atherosclerosis as indicated by the number of pluses for the cases in the particular age group.

of encroachment on the lumen and the extent of surface-area involvement were estimated. For the purposes of this study, the degree of reduction in luminal diameter by the atherosclerotic lesion was used as the basic criteria for grading the degree of coronary atherosclerosis. It has been found previously that the degree of luminal obliteration corresponds closely to the extent of surface-area involvement. Those coronary arteries that only contained flat lipid streaks were graded as plus-minus, diminution in luminal diameter up to 20 per cent was graded as 1+, up to 40 per cent 2+, and up to 70 per cent 3+. Individuals with advanced coronary atherosclerosis, in whom an accident had occurred and in whom insufficient trauma was present to account for death, were excluded because the possibility existed that coronary occlusion might have precipitated the accident. The number of such cases excluded were few and could not significantly alter the findings. The occupations of the individuals were determined by interviews with close relatives, employers of the deceased, insurance records, and the results and records of police investigations.

Those cases in which the findings at autopsy were consistent with diabetes mellitus, chronic renal disease, cirrhosis of the liver, or hypothyroidism were excluded from the study because of the possible influence of such conditions on the atherogenic process. Also eliminated were cases with a proved previous clinical history of hypertension or diabetes mellitus. The final group of cases therefore consisted essentially of white men who had no significant disease process that might, in our present state of knowledge, influence the rate of development of coronary atherosclerosis.

Men in such occupations as accountant, bank clerk, chauffeur, business executive, stenographer, were classified in the sedentary group. Those in

Table 2

*Degree of Coronary Atherosclerosis in Sudden Fatalities from Accident, Suicide, and Homicide (Physically Active Occupations)*

Age	Number of cases				Index
	Degree of coronary atherosclerosis				
	±	+	++	+++	
31—35	8	5	4	0	0.7
36—40	3	2	5	1	1.3
41—45	4	5	6	2	1.3
46—50	2	4	8	6	1.9
51—55	2	3	6	10	2.3
56—60	0	5	7	9	2.5
Total	19	24	36	28	

\*Index figures are the average degree of coronary atherosclerosis as indicated by the number of pluses for the cases in the particular age group.

such occupations as construction worker, gardener, letter carrier, and plumber, were classified in the physically active group. No reliable information was available about the physical activity engaged in during the leisure time of these individuals. Only those cases were included in which it was believed that a reliable occupational history had been obtained.

### Results

The degree of coronary atherosclerosis in 207 individuals who met the criteria was determined. One hundred of these were classified, according to their occupations, into the sedentary group, and 107 into the physically active group. In tables 1 and 2 are noted the number of cases in each age group and the degree of coronary atherosclerosis. In each age group the average degree of coronary atherosclerosis is listed in the final column under the heading "Index." In each age group the degree of coronary atherosclerosis in the 2 occupational categories was not significantly different. Figure 1 shows the degree of atherosclerosis in the 2 occupational categories at the various age levels to be similar.

### Discussion

The reported greater tendency for individuals in sedentary occupations to have myocardial infarction, and to die of it at younger ages than individuals in physically active occupations cannot be explained by significant

differences in the degree of coronary atherosclerosis at comparable age levels, according to our findings. If these results are valid, reasons are needed other than the degree of coronary atherosclerosis. Eckstein<sup>5</sup> demonstrated in experimental studies on dogs that partial coronary occlusion followed by exercise produced a significantly greater degree of intercoronary collateral anastomoses than the same grade of experimental coronary occlusion in animals that are not exercised. Lesser degrees of experimental coronary occlusion were associated with the development of anastomotic channels only when the dogs received sufficient exercise. These collateral channels were demonstrated in dogs to be anatomically similar to those observed in the human hearts of individuals who have been subjected to chronic degrees of relative cardiac anoxia. These experimental findings appear to be pertinent to the currently reported study. A partial answer to the human problem may be based upon differences in the collateral myocardial circulation in the more physically active man. Physical activity, as reflected by the type of occupation, in combination with the gradual atherosclerotic narrowing of the coronary arteries, may stimulate the development of a more efficient collateral circulation. Therefore, at any time the myocardium of the physically active man is better able to cope with any sudden or acute disturbance than that of the sedentary man with the same degree of coronary atherosclerosis, whose collateral vessels have not developed to the same extent.

This mechanism as a possible explanation for the differences in the age-specific mortality or morbidity rates from sudden coronary occlusion in different occupational groups must be considered in any investigation into the various problems concerned with prevention or treatment of coronary atherosclerosis. Clinical evaluation of so-called anti-atherosclerotic agents should be made on individuals within the same occupational grouping. Evaluations of incidence of coronary artery disease in different population groups and geographic

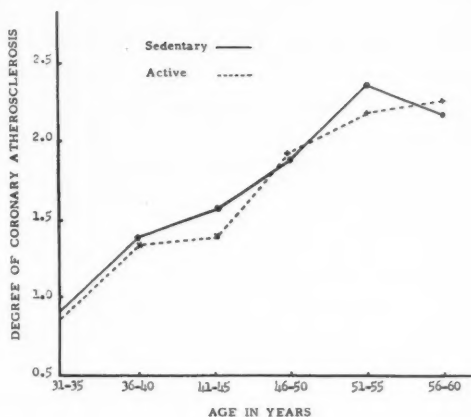


Figure 1

*Degree of coronary atherosclerosis in 2 occupational groups.*

areas, or at different periods of times, must also take this factor into account. Differences in the frequency of ischemic heart disease may be based on the state of the collateral circulation in the myocardium and not on the degree of atherosclerosis. Such differences might result from variations in the distribution of occupational categories in various areas at different time: what might be considered to be an increase in recent times in the incidence of coronary atherosclerosis might, to some extent, only reflect a shift in the nature of the working population from heavy physical labor to more sedentary occupations as a result of mechanization and automation.

In prior studies on the same series of autopsies, it has been demonstrated that the distribution of various constitutional body types is not significantly different in the sedentary and more active occupational groups. Therefore, this cannot be considered as a serious factor that might significantly influence the conclusions. Confirmation of this concept must await postmortem coronary arterial injection studies, in which the anastomoses are quantitatively measured, and in which the degree of coronary atherosclerosis has been estimated in individuals of various age levels in the different occupational categories.

### Summary

In autopsies on "normal" white men between the ages of 30 and 60, who died suddenly from accident, homicide, or suicide, there were no significant differences in the degree of coronary atherosclerosis in those engaged in sedentary occupations and those engaged in physically active occupations.

### Summario in Interlingua

In le necropsias de "normal" homines de racia blanc de etates de inter 30 e 60 annos—morte subite—mente in accidentes o per homicidio o suicidio—nulle significative differentias esseva notate in le grado de atherosclerosis coronari inter le subjectos de occupationes sedentari e le subjectos ingagiante in occupationes a activitate physie.

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We medical men never really think of ourselves as professors because we look upon university connections as opportunities for doing our own work. As for our teaching obligations, as we grow wiser we learn that the relatively small fractions of our time which we spend with well-trained, intelligent young men are more of a privilege than an obligation. For these groups are highly selected, each year more thoroughly prepared, and they force the teacher continually to renew the fundamental premises of the sciences from which his specialty takes off. It keeps us as keen as we are individually able to be, for, in a rapidly moving subject, there is a vis a tergo that keeps pushing us up, and we profit from it most directly through the fresh young blood that is pumped into our brains each year by the eager youngsters who won't stand for pedantic nonsense.

So while we are, technically speaking, professors, we are actually older colleagues of our students, from whom we often learn as much as we teach them. This, and the sense of humility that is constantly forced upon honest investigators by the incompleteness of their own small victories over the secrets of nature, keep us from developing that sense of sacred superiority that is shared by some academicians only with the monkeys of Benares.—HANS ZINSSER. *As I Remember Him*. Boston, Little, Brown & Company, 1940, p. 293. (Submitted by H. M. Marvin, M.D.)

# Retinal Vascular Reactivity in Patients with Diabetes Mellitus and with Atherosclerosis

By J. B. HICKAM, M.D., AND H. O. SIEKER, M.D.

**T**HE VASCULAR changes of diabetic retinopathy are apparent by ophthalmoscopic examination primarily in capillaries and veins.<sup>1</sup> In the absence of hypertension or the occasional occlusive lesions of atherosclerosis, the retinal arteries show little visible change.<sup>2</sup> It is reported that typical diabetic retinopathy can occur without any arteriolar lesions being evident on serial histologic examination of the retina.<sup>3</sup>

Despite the paucity of visible changes in the retinal arteries of nonhypertensive diabetic patients, observations in a few patients have shown that these vessels may fail to constrict normally when the subject breathes oxygen.<sup>4,5</sup> Impairment of this normal response in both arteries and veins of the fundus also occurs in patients with arterial hypertension, where sclerotic vascular changes are prominent. In diabetic subjects this finding indicates that the vessels may be functionally abnormal even though no lesions are evident on ophthalmoscopic examination. In order to obtain quantitative information on the loss of retinal vascular reactivity which may occur in diabetes, a comparative study has been made of the retinal vascular response to breathing oxygen in a substantial number of diabetic and control subjects. To clarify the effect of atherosclerosis upon retinal vascular reactivity, observations have also been made on patients who have clinically significant atherosclerosis in the absence of diabetes or

hypertension. It is the purpose of this paper to present the results of these studies.

## Methods and Subjects

As described elsewhere,<sup>4</sup> retinal vascular reactivity is expressed as the mean per cent shrinkage in visible diameter of retinal vessels which results from breathing oxygen for 5 minutes. Fundus photographs were made of the seated subjects while they breathed first air and then oxygen, and the visible diameter of the larger retinal arteries and veins was measured from these photographs, by means of a low power microscope with a scale in the eyepiece. From these measurements the arterial and venous reactivity, as defined above, were separately calculated.

The subjects were all hospital patients. The control group comprised 47 persons, 34 males and 13 females, ranging in age from 13 to 76 years, who were not seriously ill at the time of study and who showed no evidence of diabetes or significant cardiovascular disease.

Observations were made on 50 hospital patients with diabetes mellitus, of whom 33 were males and 17 females. The age range was from 16 to 76 years. All diabetic subjects were receiving insulin and none was significantly acidotic or markedly hyperglycemic at the time of study. Fifteen of the diabetic patients were classified as also being hypertensive by virtue of having a systolic arterial pressure which often exceeded 150 mm. Hg, a diastolic pressure which often exceeded 100 mm. Hg, or both. Of the nonhypertensive diabetic subjects, 15 had definite diabetic retinopathy, while 20 showed no definite abnormalities of the fundus. The diagnosis of diabetic retinopathy was made if any of the following was present: capillary aneurysms; neovascularization; definite venous abnormalities such as dilatation, tortuosity, and sacculatation; hemorrhages; and exudates.

Observations were also made on 15 hospital patients, 12 males and 3 females, with the clinical diagnosis of atherosclerosis, but without diabetes or hypertension. The age range was 26 to 66 years. The youngest patient was a woman with hypercholesteremia and xanthomatosis who died of a

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**Table 1**  
*Retinal Vascular Reactivity to Breathing 100 Per Cent Oxygen in Control and Diabetic Subjects*

Subjects	Number	Retinal vascular reactivity*	
		Arteries	Veins
Control (Age range: 13-76 yrs.)	47	11.3±4.3†	14.5±5.8
All diabetic (Age range: 16-76 yrs.)	50	5.7±4.6‡	10.8±5.8‡
Normotensive diabetic	35	6.3±4.8‡	11.9±5.4‡
Normotensive diabetic without retinopathy	20	8.2±4.7‡	12.8±5.3
Normotensive diabetic with retinopathy	15	3.8±3.8‡	10.8±5.5‡
Hypertensive diabetic	15	4.1±4.3‡	8.3±6.8‡

\*Expressed as per cent decrease in vessel diameter after breathing oxygen for 5 minutes.

†Means and standard deviations.

‡Significantly different from the control group.

myocardial infarction a few days after the study and who showed extensive atheromatosis at autopsy. One man, 57, had obliterative arterial disease of the lower extremities, but no other clinical evidence of atherosclerosis. Of the remainder, 6 had had a well-documented myocardial infarction and 7 had classical angina pectoris without definite evidence of infarction. In these 13 cases, records of the blood pressure were available which antedated any evidence of coronary artery disease, and all these patients had been normotensive.

For determining the significance of differences between means, the data were subjected to conventional statistical treatment.<sup>6</sup> Statistical significance was taken to begin at the level  $p = .05$ .

### Results

The data for control and diabetic subjects appear in table 1. The arterial and venous reactivity of control subjects is in good agreement with that previously reported for smaller groups of normal subjects.<sup>4, 5</sup> The diabetic data are presented for the entire group, and also for certain subgroups, divided according to the presence or absence of retinopathy and hypertension. It is notable that the arterial and venous reactivity of the diabetic is significantly less than that of the control subject, both for the total diabetic group and for each subgroup as well, with the single exception of venous reactivity in normotensive diabetic patients without retinopathy. It is also notable that the loss of arterial reactivity in diabetes is more profound in the group with

retinopathy than in uncomplicated diabetes. That is, the arterial reactivity of the normotensive diabetic subject without retinopathy ( $8.2 \pm 4.7$ ), while less ( $p < .01$ ) than that of the control group ( $11.3 \pm 4.3$ ), is still greater ( $p < .01$ ) than that of the normotensive diabetic subject with retinopathy ( $3.8 \pm 3.8$ ). Once retinopathy is present, the addition of hypertension does not produce a further significant change in reactivity.

Table 2 shows the results obtained in patients with atherosclerosis who did not have hypertension or diabetes. There is no significant difference between the arterial and venous reactivity of these patients and that of the control subjects.

### Discussion

There is abundant evidence that the small arteries, veins, and capillaries of diabetic patients may show, in various body regions, morphologic changes associated with the diabetes itself and not with the atherosclerosis or hypertension that commonly accompanies the disease.<sup>3, 7-9</sup> It has also been found that blood flow in the great toe of diabetic patients shows, on the average, less than the normal increase in response to tetraethyl ammonium chloride or indirect heating.<sup>10, 11</sup> This is a form of reduced vascular reactivity which may be analogous to that which has been presently reported for the retinal vessels

Table 2

*Retinal Vascular Reactivity to Breathing 100 Per Cent Oxygen in Atherosclerosis*

Subjects	Number	Retinal vascular reactivity	
		Arteries	Veins
Atherosclerotic without diabetes or hypertension (Age range: 26-66 years)	15	9.0±4.4	12.3±4.1

It is striking that the retinal arterioles of diabetic patients may show little or no change on ophthalmoscopic examination and yet demonstrate what appears to be severe functional impairment, as measured by marked reduction in a constrictor response which is normally present. It is likely that the ability to change blood flow in the retina by altering retinal vascular caliber in response to changes in local metabolic requirements is of considerable significance in maintaining homeostasis in this tissue, which has an extraordinarily high rate of oxygen consumption. It is possible that impairment of this homeostatic mechanism could, in itself, hasten the progression of retinopathy.

In recent years it has been pointed out repeatedly that diabetic retinopathy is not the consequence of atherosclerosis.<sup>2,3</sup> The present results indicate that atherosclerosis alone, even though productive of severe disability elsewhere, does not cause significant alterations in retinal vascular reactivity. This finding is not surprising, since uncomplicated atherosclerosis produces only occasional, isolated lesions in the retinal vessels, which are visible by the ophthalmoscope.<sup>12</sup>

#### Summary

By means of fundus photography, a comparative study has been made of the constrictor response of retinal vessels to the inhalation of oxygen in 47 control subjects, 50 diabetic patients, and 15 persons with atherosclerosis unassociated with hypertension or diabetes.

The diabetic group showed decreased reactivity of both arteries and veins, as indicated by a decreased constrictor response to oxygen. Retinal arterial reactivity was sig-

nificantly reduced in diabetic subjects, even in the absence of retinopathy or hypertension. With the appearance of retinopathy, arterial reactivity was still further reduced.

The patients with uncomplicated atherosclerosis did not show significant changes in retinal vascular reactivity.

#### Summario in Interlingua

Per medio de photographia del fundo ocular, un studio comparative esseva effectuate del responsa constrictori de vasos retinal al inhalation de oxygeno. Le casuistica consisteva de 47 subjectos de controlo, 50 patientes con diabete, e 15 subjectos con atherosclerosis sin association con hypertension o diabete.

Le gruppo de diabeticos monstrava reactivitate reduceite tanto in le arterias como etiam in le venas a judicar per le reduceite responsa constrictori al effecto del oxygeno. Le reactivitate retino-arterial esseva significativemente reduceite in subjectos con diabete, mesmo in le absentia de retinopathia o hypertension. Con le apparition de retinopathia, le reactivitate arterial esseva reduceite additionalmente.

Le patientes con non-complicate atherosclerosis non manifestava significative alterationes in le reactivitate retino-vascular.

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### Sir Dominic John Corrigan

Sir Dominic John Corrigan was born December 1, 1802, in Dublin. While still receiving his primary education, he became the demonstrator of experiments on hydrostatics and pneumatics in connection with his professors' lectures. This experience probably influenced profoundly his comprehension of the dynamics of the circulation that led to the observations on which his fame rests. After obtaining his M.D. degree from Edinburgh University in 1825, he was associated in Dublin with illustrious physicians including Adams, Carmichael, Collins, Graves, and Stokes. Six years previously Laennec had invented the stethoscope and published his book on auscultation. In 1830, at the age of 28, he became physician to the Jarvis Street Hospital, where he had control of only six beds from which "he drew the most valuable portion of his clinical experience," which was the basis of his classic treatise *On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves*. Single features of aortic regurgitation, such as the collapsing pulse, and the altered heart sounds and murmurs, had been noted by Cooper, Vieussens, and Hodgkin, but the full description and explanation of the clinical findings in terms of the underlying pathology and physiology had not been put forward in a comprehensive, interrelated manner. The great French clinician, Armand Trousseau, first designated this condition as Corrigan's disease; the French to this day still use the term "Maladie de Corrigan." He also described the Irish "famine fever" of 1847, noted the "cerebral breathing" of typhus, the expansile pulsation of aneurysm (Corrigan's sign) and cirrhosis of the lungs.

In later years, Corrigan became President of the Dublin Pathological Society, was physician to the House of Industry Hospital, was made Physician-in-ordinary in Ireland to Queen Victoria, received many honors and honorary degrees, and was created a baronet. In 1878, at the age of 76, he suffered a slight paralytic stroke, and in 1880, at the age of 78, he suffered a right hemiplegia and died on February 1, 1880.—Ed.

# Hourly Variation in Total Serum Cholesterol

By JOHN E. PETERSON, M.D., ALAN A. WILCOX, M.S., MELVIN I. HALEY, PH.D.,  
AND ROBERT A. KEITH, PH.D.

**D**URING A STUDY<sup>1,2</sup> of variations in serum cholesterol, we observed striking changes from day to day in certain subjects. In a few individuals the change in serum cholesterol was more than 200 mg. per cent from one morning to the next. In sharp contrast, in other subjects the level of serum cholesterol seemed quite stable. Similar observations have been made by Thomas and Eisenberg.<sup>3</sup> The tendency toward a labile pattern seemed to persist from one year to the next in certain subjects and it therefore seemed desirable to investigate further the rapidity with which changes might occur.

## Method and Material

The studies reported here concern hourly variations in total serum cholesterol among individuals in 2 groups of apparently healthy medical students. Group 1 consisted of 5 students who were selected because of a marked lability in serum cholesterol that each had shown during a previous period of observation. These 5 subjects are referred to later as the "labile group." Group 2 consisted of 5 other subjects whose serum cholesterol had seemed quite stable during the previous period of observation. All subjects in each group had participated in earlier studies in which serum cholesterol had been measured before and during the course of semester examinations. At least 12 determinations of serum cholesterol had been made on each subject and these were scattered over the freshman and sophomore years of medicine.

## Plan of Study

During Christmas holidays the 5 students constituting the "labile group" were hospitalized from December 29, 1958, until January 2, 1959, to facilitate observation. They were ambulatory with certain limitations imposed by the procedure and were fed a general hospital diet of approximately 2,400 calories. Lacto-ovo-vegetarian food sources

from the School of Medicine, College of Medical Evangelists, Loma Linda, Calif., and the Claremont Graduate School, Claremont, Calif.

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were used, and the diet was planned to include 75 Gm. of protein, 100 Gm. of fat, and 300 Gm. of carbohydrate. The participants were told briefly of the general plan to be followed in the study. Polyethylene catheters were placed in a brachial vein and blood samples were collected at hourly intervals from 6 a.m. until 10 p.m. and again at 2 a.m. Between samplings a slow infusion of physiologic salt solution was maintained to prevent clotting of blood within the catheter. The amount of the infusion varied a little from day to day and among the subjects, but averaged 2,400 ml. for each 24 hours.

Subsequent treatment of the 2 groups was as nearly alike as possible except for 3 points. 1. The labile group was studied during the Christmas holidays while the stable group was observed at Easter. 2. Because of technical difficulties hourly blood samples were obtained by repeated venipuncture rather than from the indwelling catheters during the first 4 hours of the experiment with the labile group. 3. The period of exposure in a cold room was omitted for the stable group.

## Day 1

The first day was used for control. The subjects were permitted to lounge about their quarters with no disturbance except for the drawing of hourly blood samples.

## Day 2

At 2 p.m. all 5 "labile" subjects were placed in a cold room with the temperature at 4 C. They remained in this environment for 45 minutes with minimal clothing to protect them from the cold. On leaving the cold room they were warmed quickly with blankets and a bath.

## Day 3

Early on the third day the subjects were told they would be introduced to a situation that would be psychologically stressful. During the morning each subject was brought in turn to the physiology laboratory. He was asked to lie on a cot and leads were attached for simultaneous recording of respiration, electrocardiographic lead II, finger plethysmography, and galvanic skin response. A microphone was then strapped about the subject's neck and rubber-covered ear phones were placed over his ears. In addition to the array of equipment some additional pressure was furnished by the presence of instructors from medicine and physiology who participated in the study.

As soon as the polygraph record was stable, the delayed auditory feedback procedure was begun. Instructions were read aloud by the subject from a card placed before him:

This test is an index of your ability to adapt to a controlled hospital routine. You will be given a number of cards to read aloud and to answer. The first set of cards will consist of proverbs for you to tell the meaning of in your own words. The second set of cards will consist of medical questions with which you should be thoroughly familiar. After you have interpreted the first three proverbs, you will begin to hear an echo of your voice. It will be your task to explain fully in spite of the echo. Remember to begin each card by reading it aloud.

On completing the interpretation of 15 proverbs under delayed auditory feedback conditions the subject then answered 5 medical questions. The delayed auditory feedback mechanism consisted of a tape recorder modified by the addition of a monitor-head and circuit. The monitor-head was set to provide a 0.30-second delay, an interval of maximum interference with normal speech delivery.

Each such test lasted for approximately 20 minutes. The behavioral reaction varied considerably from one subject to another, although each one showed some characteristic slurring of speech, unfinished words, and retardation of thought processes at the beginning of the auditory feedback. A few individuals reacted with excessive perspiration, twitching of fingers and toes, completely blocked speech pattern, grossly inadequate interpretation of proverbs, and inability to recall common medical information that was ordinarily well known by the subject. There were no consistent behavioral differences between the 2 groups, and most of the subjects seemed to adapt rather quickly to the auditory feedback simply by a slowing of their responses.

#### Day 4

This was another control day with no experimentation.

#### Day 5

At approximately 8:45 a.m. each subject was given 0.6 ml. of epinephrine subcutaneously (Adrenaline Chloride, 1:1000 solution, Parke Davis & Co.), and after 1 hour a second injection of 0.8 ml. was similarly given. Clinical signs of epinephrine effect were clearly evident in each case but none of the subjects was made seriously uncomfortable by this dosage.

#### Cholesterol Measurement

Total serum cholesterol was measured by the method of Pearson, Stern, and McGavack.<sup>4</sup> Each

blood sample was tested in duplicate and in any case in which the hourly change was marked, the determination was rechecked along with 1 or 2 samples before and after it. Each value reported in the subsequent data indicates the mean of all determinations on that sample. This method (Pearson, Stern, and McGavack) for measuring total serum cholesterol has been used in our laboratory for some time and all determinations were done by the same individuals. Technical error\* of measurement was rechecked twice during the experiment with use of 20 samples on one occasion and 21 on another. In these determinations technical error equaled 3.24 and 2.14 respectively. This amount of error compares favorably with data reported in the cooperative study of lipoprotein and cholesterol measurements.<sup>5</sup> Twenty aliquots of pooled serum submitted under code markings and along with other samples showed a range of 271 to 291 mg. per 100 ml., with a mean of 284.2 and a standard deviation of 7.59.

#### Results

Hourly variations in total cholesterol for subjects in these 2 groups are shown graphically in figures 1 and 2. At least 3 points are evident from these data. 1. Significant changes in the level of serum cholesterol may occur within a few hours in certain individuals. 2. The variation of serum cholesterol is greater and seems more consistently related to certain environmental factors among the subjects in group 1. 3. The mean level of serum cholesterol is higher for group 1, being 252.7 mg. per cent as compared to 188.4 for group 2 (table 1).

#### Control Day 1

Review of the data from group 1 shows that the level of blood cholesterol declined rather sharply a few hours after the experiment got under way. Before the chemical data were available, we questioned whether this first day could be regarded properly as a control period. In retrospect we doubt that it should be so regarded. All 5 subjects were quite apprehensive initially, and this apprehension was aggravated by technical difficulties. The

\*The technical error of measurement is  $\sigma = \sqrt{\sum d^2/2k}$ , i.e., the square root of the sum of the squared differences of duplicates divided by twice the number of pairs. This statistic was used on the advice of Dr. Sidney Abraham as a measure of duplicate reproducibility.

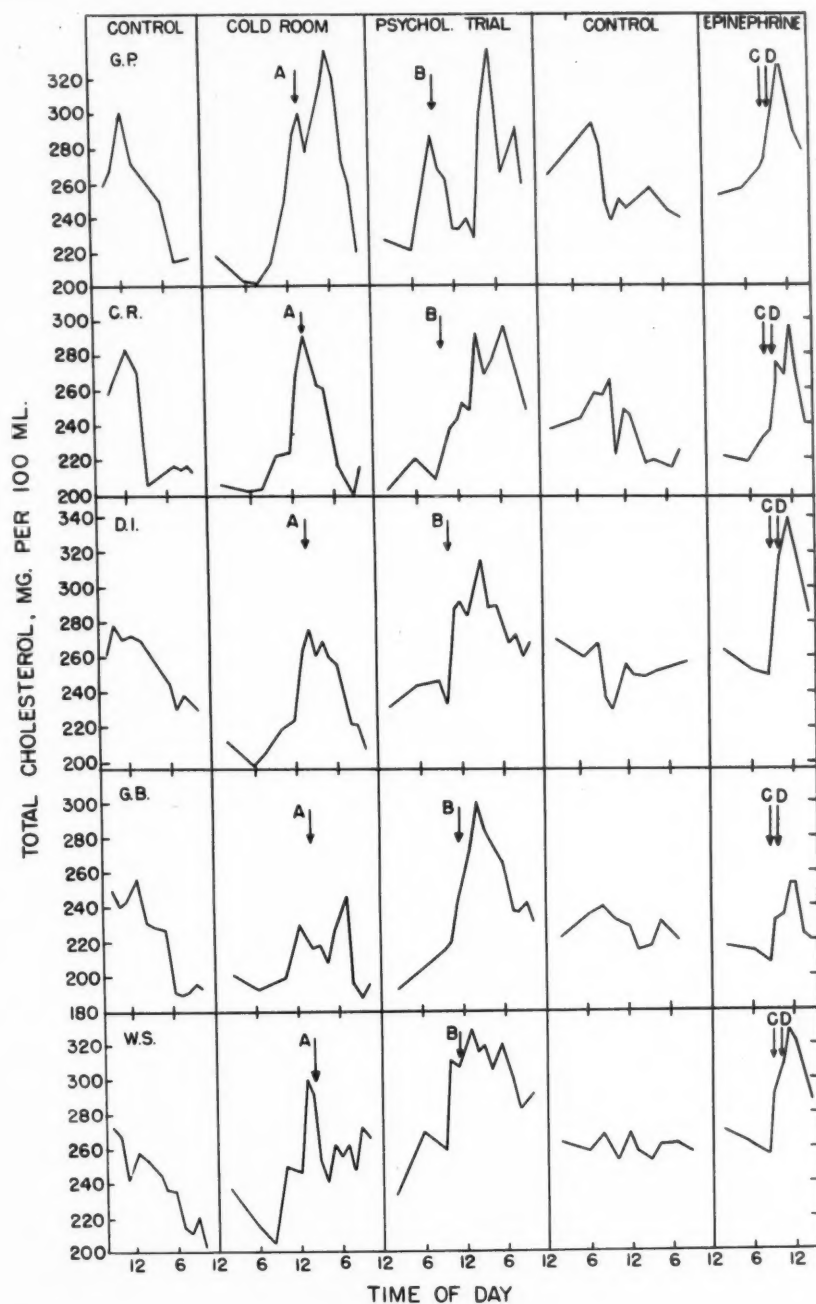


Figure 1

Pattern of hourly changes in level of serum cholesterol for 5 subjects comprising Group 1 (labile). Arrow A indicates time at which subjects entered cold room. Arrow B indicates time at which psychological test was begun. Arrows C and D indicate times at which epinephrine was injected subcutaneously.

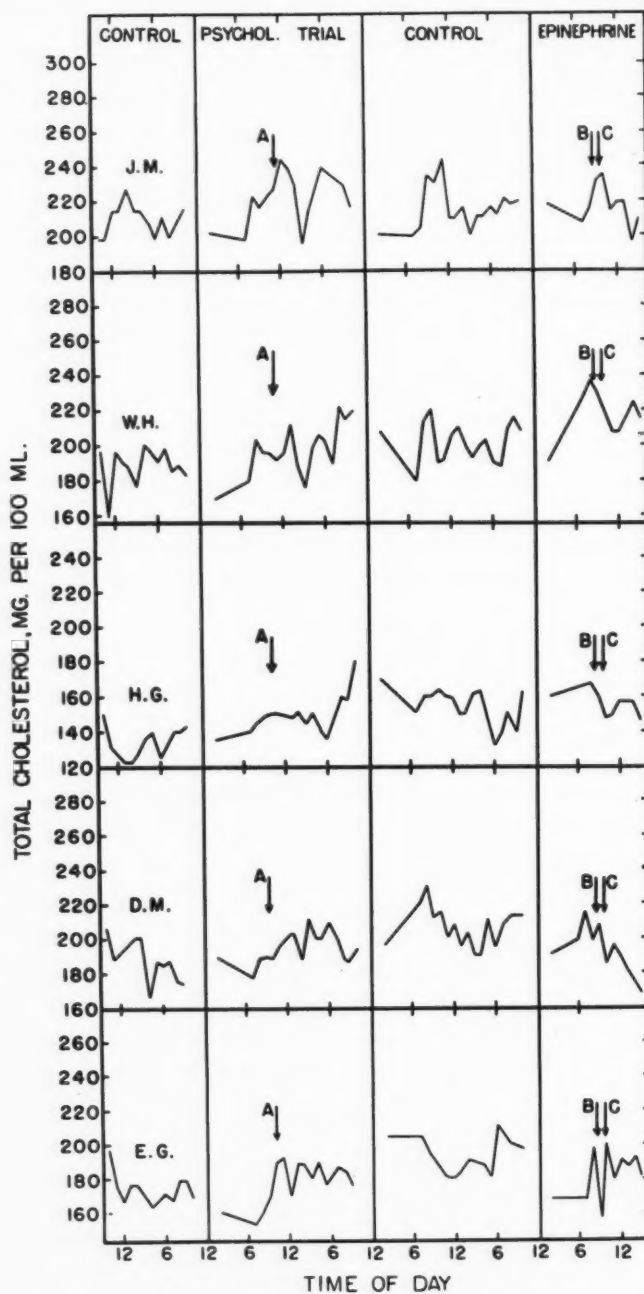


Figure 2

Pattern of hourly changes in level of serum cholesterol for 5 subjects comprising Group 2 (stable). Arrow A indicates time when psychological test was begun. Arrows C and D indicate times at which epinephrine was injected subcutaneously.

Table 1  
Mean Daily Cholesterol Levels of Individual Subjects

Subject	Control mg. % $\pm$ S.D.*	Cold room mg. % $\pm$ S.D.	Psychological trial mg. % $\pm$ S.D.	Control mg. % $\pm$ S.D.	Epinephrine mg. % $\pm$ S.D.	Total mg. % $\pm$ S.D.
Group 1						
G.P.	251.9 $\pm$ 25.9	263.3 $\pm$ 42.8	260.3 $\pm$ 30.9	256.8 $\pm$ 18.4	285.3 $\pm$ 26.8	262.9 $\pm$ 33.0
C.R.	238.3 $\pm$ 28.7	232.5 $\pm$ 30.7	248.9 $\pm$ 29.1	259.5 $\pm$ 28.3	252.9 $\pm$ 27.8	245.9 $\pm$ 28.5
D.I.	254.8 $\pm$ 18.0	235.1 $\pm$ 25.7	271.8 $\pm$ 24.1	252.9 $\pm$ 11.8	290.0 $\pm$ 29.1	259.6 $\pm$ 32.5
G.B.	219.9 $\pm$ 24.4	201.5 $\pm$ 19.3	246.7 $\pm$ 28.8	227.2 $\pm$ 8.0	228.4 $\pm$ 15.2	226.6 $\pm$ 24.6
W.S.	238.6 $\pm$ 21.7	253.2 $\pm$ 23.8	298.6 $\pm$ 27.3	260.2 $\pm$ 5.4	291.2 $\pm$ 24.5	267.8 $\pm$ 32.2
Group 2						
D.M.	188.7 $\pm$ 11.4		193.7 $\pm$ 9.1	205.4 $\pm$ 11.1	193.2 $\pm$ 12.1	196.3 $\pm$ 13.5
E.G.	173.8 $\pm$ 8.5		177.1 $\pm$ 11.8	193.1 $\pm$ 10.1	179.1 $\pm$ 13.9	181.1 $\pm$ 12.5
H.G.	133.5 $\pm$ 8.3		149.2 $\pm$ 10.5	154.0 $\pm$ 9.6	156.6 $\pm$ 6.3	148.5 $\pm$ 12.4
B.H.	187.9 $\pm$ 10.6		197.3 $\pm$ 14.7	200.8 $\pm$ 10.9	219.8 $\pm$ 12.5	201.1 $\pm$ 16.4
J.M.	209.3 $\pm$ 9.3		220.5 $\pm$ 14.3	215.0 $\pm$ 10.5	219.5 $\pm$ 11.2	216.2 $\pm$ 12.3

\*S.D.=standard deviation.

Technical error of measurement ( $\sigma_e$ )=2.25.

subjects seemed more relaxed as the day wore on, and it now appears to us that the decline in blood cholesterol somewhat paralleled this lessening of apprehension.

The experiment got under way more smoothly in the case of group 2. No technical difficulties were encountered and initial apprehension was less evident. Hourly changes in cholesterol, among this second group of subjects, were less striking, and no consistent pattern was apparent.

#### Exposure to Cold

This experiment involved only the subjects in group 1. It can be seen that blood cholesterol rose sharply before the exposure to cold, and it may be significant that these students knew of the intended procedure several hours before entering the cold room. Cholesterol levels dropped rather quickly in 3 of the 5 subjects. In 2 cases there was some secondary rise but we are unable to relate it to any observed events.

#### Psychological Trial

Changes in the level of serum cholesterol that occurred in conjunction with the delayed auditory feedback procedure are a bit more varied but all the subjects in group 1 showed some striking change. This experience appeared in most instances to be more disturbing than the subjects had expected. This is in

contrast to the previous day's experience with cold in which they commented that the exposure was "not as bad as we had expected."

Changes in serum cholesterol occurring among the subjects in group 2 were less striking and the patterns were less consistent.

#### Control Day 2

Differences between the 2 groups of subjects were less evident on this second control day. However, the average serum cholesterol for subjects in group 1 was higher than for those in group 2, and the hourly variation for 2 of the subjects in group 1 was somewhat greater than for the others (table 1). These are the 2 students who had previously shown the greatest fluctuation in serum cholesterol at the times of semester examinations.

#### Epinephrine

Each subject in our "labile" group showed a prompt rise and fall in blood cholesterol after subcutaneous injection of epinephrine. No such consistent response was seen among the subjects in group 2, and it was therefore arranged to repeat this observation on 3 of the labile subjects. Figure 3 presents the data from this experiment, which was done about 3 months later. The response was similar though a bit less marked than on the first occasion.

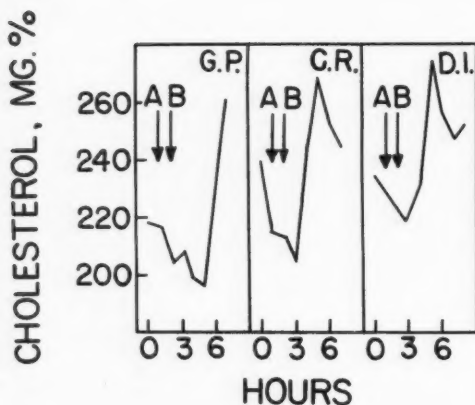


Figure 3

Re-check of hourly changes in serum cholesterol following subcutaneous injection of epinephrine in 3 subjects of Group 1. Arrows A and B indicate times at which epinephrine was given.

#### Discussion

Diurnal variations in serum cholesterol have been studied by several investigators. The majority<sup>6-9</sup> reported little change, although McEachern and Gilmour<sup>10</sup> found wide variations in the 5-hour cholesterol curves of certain individuals. They concluded, on this account, that single or haphazard measurements of blood cholesterol were of doubtful value.

The variations of serum cholesterol at longer intervals have been studied more extensively.<sup>11-14</sup> Schube<sup>13</sup> reported that blood cholesterol fluctuates differently among individuals and some observers<sup>15, 16</sup> have reported that the serum cholesterol of patients with coronary arteriosclerosis is inconstant and fluctuates widely in contrast to normal persons in whom the level is relatively stable.

The influence of stress on serum cholesterol is complicated by the difficulty in defining and limiting a stressful experience. Our data suggest that the anticipation of certain events may be related chronologically to changes in the level of serum cholesterol as easily as the events themselves. It appears to us that sham exposure will be necessary in order to clarify this point. Mann and White<sup>17</sup> reported that the physiological response to stress is a reduction in total serum cholesterol with a dis-

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proportionate fall in the esterified fraction. Others<sup>1, 18, 19</sup> believed that certain forms of emotional stress are usually associated with a sudden increase in serum cholesterol. The experiments on which these differing views are based are so dissimilar that there might be several reasons for the apparently differing response. The rapid and variable changes in serum cholesterol in our subjects suggest that the nature of a stressful experience, the timing of cholesterol determinations, and the preselection of experimental subjects all might influence such results.

Preselection of subjects is thought to account for the striking and rather consistent cholesterol patterns in our group 1. It should be emphasized that each subject participating in this study of hourly changes was selected because of apparent lability or stability of his blood cholesterol during previous observations which extended over a period of 2 years. Those showing the most striking changes in cholesterol at the time of semester examinations were assigned to group 1. For contrast, the subjects in group 2 were those whose cholesterol levels had shown relatively little fluctuation during the same period of time. It now appears that we might have been able to distinguish between these 2 groups of students by noting the changes in serum cholesterol after injection of epinephrine. We are not certain that this would be true of a larger group or even of these same individuals over a longer period of time. It is planned to repeat such tests with these same subjects and also to extend the studies to include a larger number of persons.

These observations support the view that the level of serum cholesterol is more variable in some individuals than in others. They also indicate that remarkable changes may occur with greater rapidity than we had supposed. The data suggest that certain situations appearing potentially to be stressful may induce rather striking changes in serum cholesterol within a few hours in selected individuals. It remains to be seen whether lability or stability will continue to be characteristic

of these persons. We are unable at this time to relate these patterns to any evidence of vascular or other disease and can only speculate about the mechanisms by which such rapid changes may occur.

### Summary

Evidence is presented to indicate that the level of serum cholesterol in certain individuals may vary widely within a matter of hours.

The data suggest also that a rapid fluctuation of the serum cholesterol level may be induced in some persons by modifying certain aspects of their environment.

Varying lability of the level of serum cholesterol and the differing response of individuals to certain environmental factors require that careful attention be given to the sampling methods used in research.

### Summario in Interlingua

Es presentate observationes que indica que le nivello del cholesterol serral in certe subjectos pote variar extensemente intra alicun horas.

Le observationes etiam suggere que un fluctuation rapide del nivello de cholesterol serral pote esser inducite in certe subjectos per le modification de certe aspectos de lor ambiente.

Varie grados de labilitate del nivello de cholesterol serral e le varietate de responsas del parte de varie subjectos a certe factores del ambiente demanda que le plus circumspecte attention es prestate al methodos de specimenage usate in investigationes scientificas.

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# Ventricular Septal Defect with Patent Ductus Arteriosus

## A Clinical and Hemodynamic Study

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**W**ITHIN the past 3 years, during cardiac catheterization performed for diagnostic studies, 18 patients were found who showed evidences of a ventricular septal defect with an associated patent ductus arteriosus. Four additional patients with this combination of lesions were discovered in a review of our files. In a survey of the literature isolated or unsubstantiated reports of such an association were found,<sup>1-5</sup> but no sizable groups of patients with ventricular septal defect and patent ductus arteriosus have been reported.

It therefore seemed worthwhile to describe the clinical and hemodynamic characteristics of these 22 patients and to discuss the therapeutic implications of this combination of lesions.

### Materials and Methods

Twenty-two patients in whom the presence of a ventricular septal defect and a patent ductus arteriosus could be proved by cardiac catheterization form the basis of this report. Two had associated coarctation of the aorta (nos. 2 and 3), and 3 additional infants showed evidences of mild or moderate pulmonic stenosis (nos. 11, 14, and 22).

The patients' ages ranged from 2 months to 20 years and 4 were under 1 year (table 1). There were 13 girls and 9 boys in the group. All patients had been admitted to the Sharon Cardiovascular Unit of the Children's Medical Center. All were examined by at least one of the authors. Several 12-lead electrocardiograms were obtained

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in each case. The tracings taken at the time of cardiac catheterization were analyzed in detail and the others were used for comparison. Roentgenograms (posteroanterior and oblique) were obtained on all patients, and fluoroscopic examinations were performed in the Radiology Department of the Children's Medical Center. Right heart catheterization by the technic previously described<sup>6</sup> has been performed in all patients, and cineangiograms, indicator-dilution curves (with indocyanine-green) and retrograde catheterization of the left ventricle were performed in selected individuals. Five patients had catheterization studies before and after surgical correction; 3 had 3 catheterization studies each, but 1 of these (no. 1) had not been studied prior to the division of his patent ductus arteriosus.

Postmortem examinations were available in 2 patients.

### Observations

#### Clinical History

The gestational history was possibly significant in 3 instances: the mothers of 2 children had rubella and 1 had "Asian flu" in the first trimester of pregnancy. Five of the infants were born prematurely.

Feeding difficulties, failure to thrive, and dyspnea were the presenting symptoms. Eight patients had at least 1 episode of pneumonia and 11 others had frequent upper respiratory infections. Congestive heart failure was diagnosed in 9, and 7 of these were under 8 months of age.

#### Physical Examination

On physical examination, it was obvious that these patients were grossly undernourished; only 1 was above the tenth percentile on the developmental weight chart. The retardation in height was somewhat less striking, but only 6 were above the tenth percentile for height.

Table 1

*Age Distribution of Twenty-two Patients with Ventricular Septal Defect and Patent Ductus Arteriosus*

Age (years)	No. of patients
0 - 1	11
1 - 5	5
5 - 10	3
10 - 15	0
15 - 20	3

Table 2

*Pulse Pressure Distribution*

mm. Hg	No. of patients
30 - 39	2
40 - 49	2*
50 - 59	5
60 - 69	4
70 - 79	1
80 - 89	4
90+	1
Flush pressures: 3 patients	
Total	19

\*Case 3 had previous division of patent ductus arteriosus.

Minimal cyanosis at rest with definite accentuation after crying was noted in 3 patients. The pulse pressure in all instances recorded (19 of 22 patients) was greater than 30 mm. Hg and was above 50 mm. Hg in 15 of 19 (table 2). Left thoracic prominence was common, and a systolic thrill along the left sternal border was present in 9 patients. The cardiac impulse was hyperdynamic in all and involved both the left and right ventricles in most instances, but isolated left and right ventricular impulses also occurred.

On auscultation the first sound seemed unremarkable. The second sound was consistently accentuated over the pulmonary area. A third sound at the apex was noted in 19 patients. A murmur was usually first discovered during the first 6 months of life but in no instance was one heard at birth. Only 2 patients had a typical continuous Gibson murmur (nos. 1 and 15). All the others had harsh systolic murmurs of grade III to VI intensity at the midsternal or, rarely, the

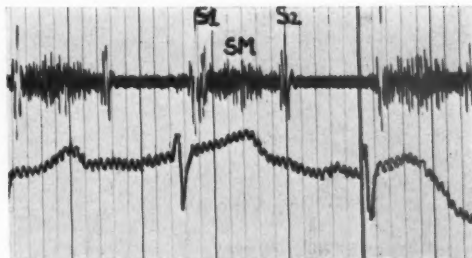


Figure 1

*Phonocardiogram of patient no. 19 taken over the fourth left sternal border, logarithmic tracing. The harsh regurgitant systolic murmur begins with the first sound. No clear-cut diastolic murmur is discernible. This tracing is compatible with an isolated ventricular septal defect. The pulmonic area tracing was even less impressive.*

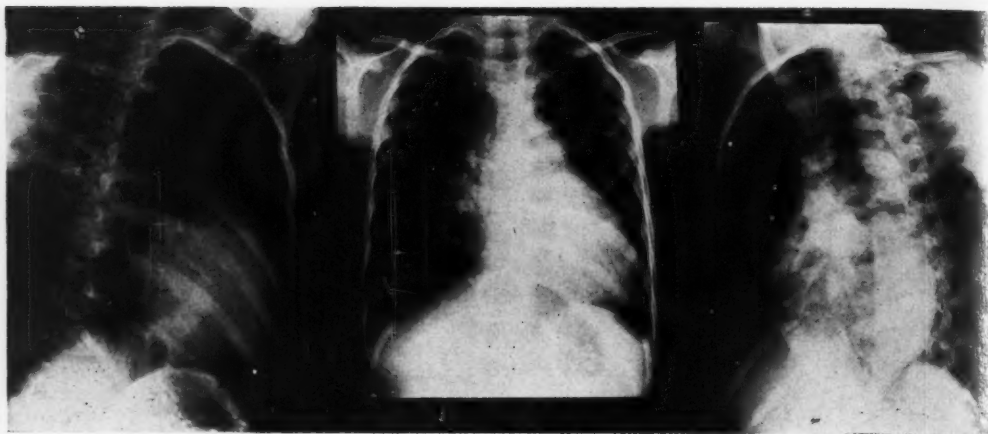
upper left sternal border (fig. 1). All 22 patients had apical mid-diastolic flow rumbles.

#### Electrocardiogram

The mean electrical axis in the frontal plane varied widely, ranging from  $-75$  to  $+165$  degrees, with 19 of the 22 having axes between  $+60$  to  $+165$  degrees. Only one patient had normal electrocardiogram (no. 14). Nineteen patients showed right ventricular hypertrophy alone or in combination with left ventricular hypertrophy, but only 2 children had pure left ventricular hypertrophy. Nine patients had evidence of left atrial enlargement alone or in combination with right atrial enlargement and only 2 showed pure right atrial enlargement.

#### Roentgenogram

All patients showed roentgenographic evidences of cardiac enlargement, which was mild to moderate in 9 and severe in the others. The enlargement involved both ventricles (the left usually predominating) in seventeen instances, whereas 2 showed pure right and 3 pure left ventricular enlargement. Left atrial enlargement could be demonstrated in 19 patients. The main pulmonary artery segment was prominent, often markedly so, in 16. Active pulmonary vascular engorgement was thought to be present in all patients, but expansile pulsations of the intrapulmonary vessels or "hilar dance" were noted in only 6



**Figure 2**

*The most common appearance of the heart as observed in 12 patients was selective enlargement of the left ventricle and left atrium, prominent pulmonary artery, and pulmonary vascular engorgement as illustrated in this child when first seen at age 7 (patient no. 1).*

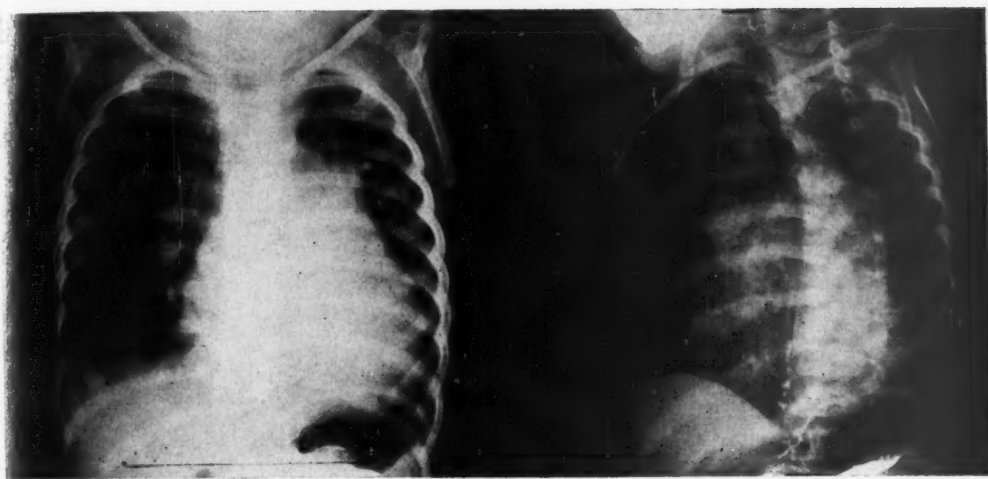
of these. In 4, additional passive congestion was thought to be present (figs. 2 to 4). With the exception of the infants in cardiac failure, the amplitude of pulsation of the left ventricle by fluoroscopy was increased. Similarly, the main pulmonary artery segment frequently showed a hyperactive beat, characterized by increased amplitude of pulsations, and in most patients the aorta shared in this hyperactivity. Fluoroscopically then, there appeared to be no definite pattern to differentiate these cases from those with an uncomplicated ventricular septal defect or patent ductus arteriosus.

#### **Hemodynamic Studies**

The diagnosis of ventricular septal defect was proved during cardiac catheterization by passage of the catheter from the right ventricle to the left ventricle or aorta in 7 instances (table 3). In 13 additional patients an increase in the oxygen saturation from the right atrium to the right ventricle of at least 10 per cent was considered strongly suggestive of a ventricular septal defect. The significance of this figure is based on observations in our laboratory of increases in oxygen saturation from the right atrium to the right ventricle in normal subjects and in patients

with patent ductus arteriosus. In 1 of the 2 remaining patients (no. 12) a ventricular septal defect was proved by right heart catheterization performed a second time after division of the ductus. In the remaining patient (no. 15) retrograde arterial catheterization of the left ventricle and indicator-dilution curves strongly suggested, but did not prove, the presence of a ventricular septal defect. In this context, we wish to emphasize the paramount importance of obtaining samples not only from the body of the right ventricle, but also from the outflow tract where increases in the oxygen saturation are most usually demonstrable. Furthermore, the significance of even smaller rises in oxygen saturation increases with the number of samples.<sup>6</sup>

The presence of the patent ductus arteriosus was proved by the passage of the catheter through it in all but 4 of the patients. In one of these, (no. 1) the diagnosis of patent ductus arteriosus was made clinically on the basis of a machinery murmur over the second left interspace, and in the other 3 it was not suspected until operative repair of the ventricular septal defect was undertaken. Whereas the oxygen saturation data were re-



**Figure 3**

*Twenty-month-old child (patient no. 15) with roentgenograms showing balanced right and left-sided enlargement, prominent main pulmonary artery segment, pulmonary vascular engorgement, and left atrial prominence. These findings were observed in 6 patients.*

cisive in suggesting a ventricular septal defect in these patients, critical increases in oxygen saturation at the ductal level (greater than 6 per cent) were present in only 5 patients. Thus the diagnosis of a patent ductus arteriosus could not have been made without the passage of the catheter from the pulmonary artery to the aorta.

The size of the left-to-right shunt through the defects was usually appreciable. All but one had a pulmonary: systemic flow ratio of at least 2:1 and many ranged up to 5:1 (the lack of accuracy of these high pulmonary flows is obvious). Calculation of the quantitative relationship between the ductal and ventricular septal defect shunt is difficult and fraught with error because of the high oxygen saturation of the right ventricular blood sample. Recognizing the limitations of these calculated figures, we may point out that in only 6 patients did the ductal shunt seem larger than that through the septum.

Arterial unsaturation was present in 13 patients. Left atrial or pulmonary venous unsaturation was proved in 6 of these (nos. 12, 13, 18, 20, and 22). Consequently, we may assume that a right-to-left shunt at the

ventricular or ductal level occurred in 7 patients.

Right atrial pressures were within normal limits in all but 2 patients. There was no gradient across the pulmonary valve except in 3 instances (nos. 11, 14, and 22). Pulmonary artery mean pressure was above 30 mm. Hg in all but 3 cases. Pulmonary capillary wedge or left atrial pressures were obtained in 18 patients and were above 6 mm. Hg in all. Pulmonary vascular resistance per square meter of body surface area was calculated in all and was above the maximal normal value of 3 units in 9 patients; 1 value (no. 15) was markedly elevated, indicating severe pulmonary vascular obstruction.

#### Course

Attempts at surgical correction of these defects were undertaken in 13 patients (table 4). Division (8 cases) or ligation (1 case) of the ductus was the only procedure performed in 9 patients, whereas in the other 4 both defects were closed. Of the latter group 1 patient (no. 1) had a 2-stage procedure 7½ years apart, and in the other 3 the ductus was an incidental finding during surgery per-

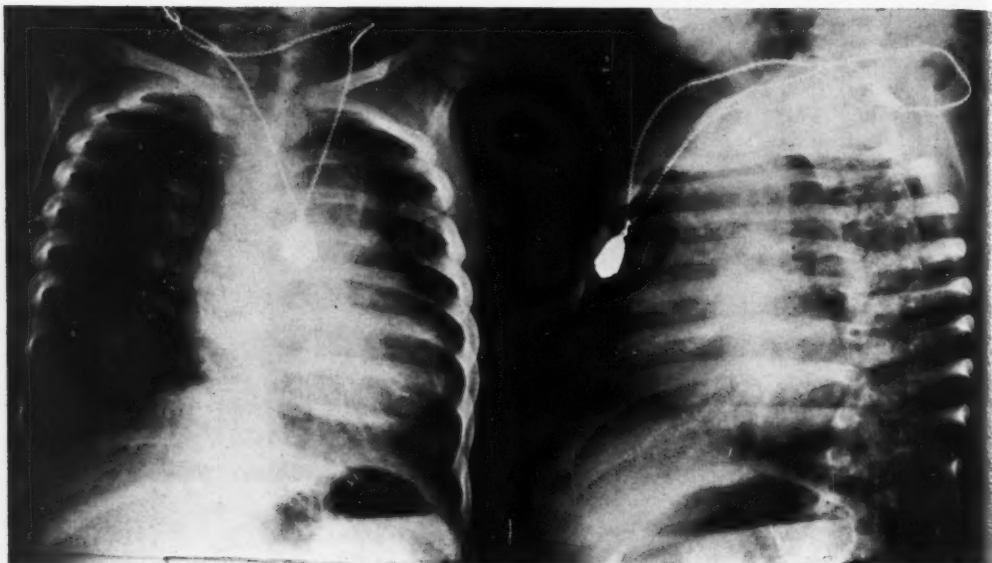


Figure 4

*Preoperative posteroanterior and left anterior oblique roentgenograms of patient no. 3, age 3 years, showing dominance of the right ventricle with prominence of the main pulmonary artery segment and pulmonary vascular engorgement.*

formed for correction of a ventricular septal defect.

The indications for surgery in 3 of the 4 patients with attempted complete correction were those currently used for surgery in ventricular septal defect, viz., symptoms of heart disease, cardiac enlargement, and a large left-to-right shunt in a child over 25 to 30 lbs. in weight.<sup>7</sup> The fourth patient in this group was operated upon for a ductus without previous catheterization on the basis of a typical Gibson murmur (no. 1). Two of these 4 patients (nos. 1 and 5) survived the operative procedure and have markedly improved both from the clinical and hemodynamic viewpoint (table 5). The 2 who died in the immediate postoperative period both had massive hemorrhage through an unsuspected patent ductus arteriosus during the time on cardiac bypass. The ligation of the duct through a midsternal thoracotomy was technically difficult, and thus the procedures were unduly prolonged, resulting in severe anoxia, marked blood loss, and persistent

generalized oozing of blood. The patient who survived the combined procedure (no. 5) also had an unsuspected patent ductus arteriosus, but ligation of the ductus was more easily accomplished while on cardiac bypass and the complications were fewer.

The indication for closing the patent ductus arteriosus in the other 9 patients without attempting to correct the ventricular septal defect simultaneously was based upon the same clinical and physiologic criteria as cited above with the exception that the patients weighed considerably less than 30 pounds. The selection of these 9 patients with known combined defects out of the 18 such patients was based upon a number of factors. In 1956, when the first 2 patients with combined lesions were discovered, division of the patent ductus arteriosus was advised in both. As seen in tables 4 and 5, no clinical improvement ensued and repeat catheterization studies revealed a significant rise in pulmonary vascular resistance. This experience made us re-evaluate our criteria for operation in 1957.

Table 3

## Preoperative Catheterization Data

Patient	% Oxygen saturation					Pressures		Flows	Resistance	Catheter passed through		Vein for cath.
	RA	RV body	RV outflow	PA	Arterial	PA mm. Hg	PC or LA mean mm. Hg	$Q_p/Q_s$	Pulmonary mm. Hg/L./min./M. <sup>2</sup>	PDA	VSD	
1*	73	84	—	86	98	65/25 (45)	19	2/1	3.4	o	o	MC
2	69	82	87	93	99	90/45 (63)	16	4.5/1	2.6	x	o	MC
3	50	60	77	81	90	74/46 (56)	14	1.5/1	7	x	x	Ax
4	64	92	93	93	96	93/42 (77)	20	4.4/1	3.1	o	o	MC
5	65	81	82	86	94	88/52 (65)	—	2.8/1	4.0	o	o	MC
6	54	77	—	79	94	100/54 (71)	24	2.9/1	5.5	x	o	Ax
7	62	88	87	89	96	87/32 (57)	20	3.2/1	4	x	o	S
8	58	67	—	82	90	90/36 (57)	8	2.7/1	5	x	x	S
9	58	77	—	84	92	77/19 (39)	10	2.8/1	3.4	x	x	S
10	73	92	85	87	95	50/15 (25)	13	2.8/1	0.9	o	o	MC
11	56	72	70	80	90	70/35 (52)	22	3.5/1	1.9	x	o	S
12	56	67	66	84	89	80/40 (60)	13	5.5/1	1.5	x	o	S
13	48	67	72	80	86	58/27 (40)	8	5.6/1	0.89	x	x	S
14	54	63	72	82	91	75/36 (54)	15	2.8/1	3.1	x	o	S
15	68	74	72	78	83	102/50 (78)	—	2/1	14.1	x	o	S
16	68	76	73	86	93	60/20 (35)	—	3/1	1.3	x	x	S
17	53	77	71	83	91	60/13 (40)	13	5/1	0.5	x	o	F
18	49	75	76	80	90	63/35 (48)	6	4.7/1	2.5	x	o	S
19	57	85	87	83	94	48/14 (24)	—	3.4/1	1.0	x	x	S
20	62	80	82	83	93	36/12 (26)	9	2.7/1	0.9	x	o	S
21	49	78	78	85	94	69/27 (46)	22	5.7/1	1.1	x	x	S
22	66	83	81	85	91	38/16 (29)	8	4/1	0.5	x	o	S

\*Preoperative ventricular septal defect; patent ductus divided without catheterization.

Abbreviations: MC, median cubital vein; Ax, axillary vein; S, saphenous vein; F, femoral vein (all right side); RA, right atrium; RV, right ventricle; PA, pulmonary artery; PC, pulmonary capillary; LA, left atrium;  $Q_p/Q_s$ , ratio of pulmonary to systemic flow; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

Of the 6 patients with combined lesions discovered in 1957, only 2 of the small infants (nos. 8 and 9) with the severest heart lesions were referred for division of the ductus alone. One of these two died and the other improved clinically. Both defects were treated in 2 older children with similar results. The remaining 2 infants were treated medically only, and both showed clinical improvement. During 1958-1959, when 12 new patients were diagnosed, only the 5 with the largest shunts who did not improve with vigorous medical therapy were subjected to operation. The results were still far from encouraging. One of the 5 improved, 2 deteriorated, 1 died, and no adequate followup is available on the remaining 1.

A survey of the surgical results in all patients, with partial or complete corrections,

suggests that (1) closing both defects has resulted in the loss of 2 of the 4 patients, but the survivors have improved significantly, and (2) closing the patent ductus arteriosus alone resulted in the loss of 2 of 9 patients, and appreciable clinical improvement was noted in only 2 of 7 survivors. Five of the 7 were recatheterized: 3 (nos. 2, 3, and 12) showed marked rise and 2 (nos. 9 and 11) showed no change in calculated pulmonary resistance. In the latter 2 patients the pulmonary: systemic flow ratio was unchanged after operation, whereas in 2 of the other 3, a significant decrease in the pulmonic flow was demonstrated. The left atrial pressure was unchanged in 1 and decreased in 2. It seems justified then, to say that surgical correction of the ductus alone is hazardous and not likely to result in significant improvement.

Table 4

*Course of Twenty-two Patients with Ventricular Septal Defect and Patent Ductus Arteriosus*

Case no.	Catheterization			Dominant L → R shunt		Type of therapy		Course			
	Date	Wt.	Q <sub>p</sub> /Q <sub>s</sub>	VSD	PDA	Medical	Surgical	Improved	Unchanged	Worse	Died
1	1950		2:1	x	divided		PDA + VSD	x			
2	1956	22	4.5:1		x		PDA			x	
3	1956	10	1.5:1	—	—		PDA			x	
4	1957	85	4.4:1	x			PDA + VSD				x
5	1957	33	2.8:1	x			PDA + VSD	x			
6	1957	15	2.9:1	x		x		x			
7	1957	25	3.2:1	x		x		x			
8	1957	9	2.7:1	—	—		PDA				x
9	1957	13	2.8:1	—	—		PDA	x			
10	1958	81	2.8:1	x			PDA + VSD				x
11	1958	15	3.5:1	x			PDA		?	—	?
12	1958	9	5.5:1		x		PDA			x	
13	1958	7	5.6:1	x			PDA				x
14	1958	12	2.8:1	—	—	x		x			
15	1958	27	2:1	—	—	x			x		
16	1958	8	3:1		x	x			x		
17	1958	11	5:1		x		PDA	x			
18	1958	9	4.7:1	x		x		x			
19	1959	10	3.4:1	x		x		x			
20	1959	7	2.7:1	x		x			x		
21	1959	9	5.7:1		x	x		x			
22	1959	8	4:1		x		PDA			x	

See table 3 for key to abbreviations.

Medical management alone was given to 9 patients. Although these patients were probably not the most severely ill of the series, and by definition responded to initial medical therapy, it is still significant that all of these patients are alive at the time of writing. Clinical improvement was noted in 6, and the condition was unchanged in 3. The details of medical management are not thought to be pertinent to this report. Suffice it to say, most of these patients received digitalis, antibiotics when necessary, and, occasionally, diuretics.

#### Discussion

On the basis of the present report, we may state that the combination of ventricular septal defect with patent ductus arteriosus is not very uncommon. Accurate estimation of the frequency of occurrence cannot be made at this time. The apparent increase in the frequency of this combination in 1958 was the

result of 2 factors, i.e., the interest in catheterizing small infants and the routine catheterization of all ventricular septal defects prior to corrective surgery.

Among the patients clinically diagnosed as having a typical patent ductus arteriosus, a ventricular septal defect may be suspected by the discovery of a separate, harsh regurgitant murmur along the left lower sternal border. Unfortunately this sign is almost wholly unreliable, since many patients, particularly infants with large ducti, may have such a murmur,<sup>8</sup> possibly due to atrioventricular regurgitation. In our opinion, such patients should have their ductus treated surgically and the ventricular septal defect, if present, may be corrected at a later date. The assumption is thus made that in the presence of clear-cut clinical evidences of a patent ductus arteriosus, particularly a Gibson continuous murmur, the shunt through the ductus must

Table 5

Preoperative and Postoperative Catheterization Data

Patient		% Oxygen saturation					Pressures		Flows	Resistances
		RA	RV body	RV outflow	PA	Arterial	PA mm. Hg	PC or LA mean mm. Hg	Q <sub>P</sub> /Q <sub>S</sub>	Pulmonary mm. Hg/ L./min./M. <sup>2</sup>
1	Post-op. PDA. 6/16/50	73	84	—	86	98	65/25 (45)	19	2/1	3.4
	7/3/57	70	91	85	86	98	45/14 (30)	13	1.4/1	1.1
	Post-op. VSD 12/19/58	70	69	71	71	97	22/10 (13)	4	1/1	3
2	Pre-op. 3/28/56	69	82	87	93	99	90/45 (63)	16	4.5/1	2.6
	Post-op. PDA 7/3/57	70	77	83	84	97	144/64 (100)	16	1.9/1	11.7
	11/19/58	70	71	70	79	95	132/62 (96)	16	1.3/1	14.4
3	Pre-op. 6/15/56	50	60	77	81	90	74/46 (56)	14	1.5/1	7
	Post-op. PDA 6/17/58	62	63	73	72	85	110/70 (90)	6	1.1/1	19
5	Pre-op. 5/28/57	65	81	82	86	94	88/52 (65)	—	2.8/1	4
	Post-op. VSD and PDA 7/2/58	65	66	67	65	95	31/15 (22)	9	1/1	2.9
9	Pre-op. 11/7/57	58	77	—	84	92	77/19 (39)	10	2.8/1	3.4
	Post-op. PDA 7/10/58	59	87	—	85	96	38/18 (26)	7	2.8/1	2.1
11	Pre-op. 2/27/58	56	72	70	80	90	70/35 (52)	22	3.5/1	1.9
	Post-op. PDA 4/3/58	67	69	82	82	90	58/20 (39)	—	3.3/1	2.9
12	Pre-op. 3/4/58	56	67	66	84	89	80/40 (60)	13	5.5/1	1.5
	Post-op. PDA 6/9/58	56	59	66	69	84	155/55 (75)	—	2/1	9.1

See table 3 for key to abbreviations.

be large enough to deserve closure. The hazard of such an operation in the face of a ventricular septal defect should not be significantly higher than that associated with patent ductus arteriosus division alone. This opinion is confirmed by other observations.<sup>5</sup>

If the patent ductus arteriosus is discovered at catheterization, by passage of the catheter through it or by oxygen saturation studies, the presence of an additional ventricular septal defect can be suspected if the right ventricular outflow blood sample is more than 5 per cent higher than the right atrial or right ventricular body sample although the possibility of pulmonic regurgitation obviously cannot be excluded with certainty.

In patients with the clinical diagnosis of a

ventricular septal defect, the presence of an additional patent ductus arteriosus may be strongly suspected at the bedside if the pulse pressure is over 50 mm. Hg. The character or location of the murmur is of no significance in the small infant but in children the maximal location of the murmur higher up along the left sternal border and the occasional suggestion of a continuous character may be of some assistance. The electrocardiograms were, on the whole, indistinguishable from those with isolated ventricular septal defects, but the roentgenograms were helpful in that almost all of these patients had some left atrial enlargement and the majority showed a prominent main pulmonary artery segment.

Since all patients with clinically suspected ventricular septal defects now undergo car-

diac catheterization prior to surgery, the hemodynamic features are much more important in this group than the clinical characteristics. In this respect, it is fortunate that the catheter traverses the ductus in many instances, particularly if the saphenous approach is used. Upon failure to demonstrate a ductus by this means, its presence should be suspected if the increase in oxygen saturation from the right ventricular outflow tract to the pulmonary artery is greater than 5 per cent.

The management of patients with clinical and physiologic diagnosis of a ventricular septal defect with patent ductus arteriosus is much more difficult than that of the group with clear-cut patent ductus arteriosus and questionable ventricular septal defect. In the latter group the patent ductus appears dominant and is significant enough alone to warrant surgical closure. In the former group, the optimal therapy appears to be simultaneous closure of both defects if technically feasible at an acceptable mortality rate. In small infants in whom combined closure presents a high risk at present, medical management should be given an adequate trial before surgery is attempted. Only if vigorous anticongestive measures fail to accomplish clinical improvement, should division of the ductus alone be undertaken. The disadvantages of ductal surgery under these circumstances, in addition to the relatively high mortality rate, are the lack of clinical improvement, failure to lower the pulmonary resistance, and, in some, the persistence of a left-to-right shunt of a magnitude comparable to the preoperative one through the ventricular septal defect alone. Our observations regarding pulmonary artery hypertension and calculated pulmonary vascular resistances after division of the ductus alone do not confirm those of others who have found that closure of the ductus prior to the septal defect results in a lowering of the pulmonary hypertension, thereby decreasing the surgical risk for later closure of the ventricular septal defect.<sup>5</sup> In our series, 3 patients (nos. 2, 3, and 12) had a striking increase in the

calculated pulmonary vascular resistance and a lowering of the pulmonary flow. Two patients (nos. 9 and 11) showed little or no change in the pulmonary flow or the calculated resistance.

Closure of the ventricular septal defect and ligation of the patent ductus arteriosus is the preferred procedure if the technical difficulties can be overcome. The influence of the combined operation on the pulmonary vasculature is not known; the scanty data available in the literature and the few observations of our own on patients with ventricular septal defect indicate that the pulmonary artery pressure probably drops in the majority commensurate with the decrease in pulmonary flow, and the calculated resistance stays the same. At best it may be hoped that the progression of pulmonary vascular changes may be halted by this procedure, even if the existing obstruction is rarely eliminated. The reason for the difference in behavior of the pulmonary vasculature post-operatively after ligating the ductus alone, as against the closing of both defects, is not known.

#### Summary

Twenty-two patients with the combined lesions of ventricular septal defect and patent ductus arteriosus, proved at cardiac catheterization, are reviewed in detail in regard to their clinical profile, hemodynamic data, and indications for, and results of, surgical repair.

The incidence of this combination of lesions is not so uncommon as would be anticipated by the paucity of the reports in the medical literature. The diagnosis of both lesions is important for management and surgical technique.

The striking findings by physical examination are the gross undernourishment and the wide pulse pressure in the great majority. Almost all have harsh systolic murmurs along the mid left sternal border and only 2 had continuous Gibson murmurs. Consequently, auscultation is of little help in delineating the presence of an associated patent ductus arteriosus.

The electrocardiogram is of minor importance in the diagnosis of this combination of lesions. Roentgenograms in the majority show features common to either lesion alone although the frequency with which left atrial enlargement is found appears to be greater in this combination of lesions.

Careful hemodynamic studies are crucial in the diagnosis of these 2 lesions. At the ductal level passage of the catheter establishes the diagnosis, or an increase in oxygen saturation greater than 5 per cent in comparison to the right ventricular blood strongly suggests the presence of a patent ductus arteriosus. The great majority of the ventricular septal defects were diagnosed by an increase in the oxygen saturation of 10 per cent or greater at the ventricular level. Almost all had pulmonary artery hypertension.

Thirteen patients had surgical intervention; 9 had only closure of the patent ductus arteriosus alone and 4 had complete repair of the lesions. In the former group there were 2 deaths and 2 improved significantly. In the latter group there were 2 surgical deaths and 2 were markedly improved. The 2 surgical deaths appear to be directly related to the massive hemorrhage through the unsuspected patent ductus arteriosus while on cardiac bypass and the subsequent technical difficulty of closing both defects from an anterior thoracotomy.

The relationship of calculated pulmonary vascular resistance to surgical closure of the defects is discussed.

It is suggested that if the patent ductus arteriosus is diagnosed on the basis of a typical machinery murmur, correction of this lesion is indicated, irrespective of the associated ventricular defect. If, on the other hand, the clinical picture is suggestive of a ventricular defect alone and the presence of the combination of lesions is discovered only at catheterization, then simultaneous correction of the 2 lesions is recommended. In small infants in whom the combined operation is particularly difficult at the present time, a

preliminary trial of medical management is recommended; only if this fails to accomplish the expected result should division of the ductus be undertaken.

#### Acknowledgment

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#### Summario in Interlingua

Le casos de 22 patientes con le combine lesions de defecto ventriculo-septal e patente ducto arteriose —omnes confirmate per catheterismo cardiac—es revistate in detalio con respecto al profilo clinic, al datos hemodynamic, e al indicationes pro reparo chirurgic e al resultados obtenite per illo.

Le occurrentia del duo lesiones in combination non es tanto incommun como on poterea supponer lo super le base del paucitate del reportos in le litteratura medical. Le diagnose del presentia de ambe lesiones es importante ab le puncto de vista del programma de tractamento e del technica chirurgic.

Le plus frappante constatationes in le examine physics es le marcate subalimentation e le alte pression differential in le grande majoritate del casos. Quasi omne le patientes ha aspere murmures systolic al longo del margine meso-sternal sinistre. Solmente 2 habeva continue murmures de Gibson. Per consequente, le auscultation es de pauc valor in delinear le presentia de un associate patente ducto arteriose.

Le electrocardiogramma es de minor signification in le diagnose de iste combination de lesiones. In le majoritate del casos, le roentgenogramma revela aspectos que es frequente in le presentia del un o del altere lesion sol, ben que le frequentia del constatacion roentgenographic de allargamento sinistro-atrial pare esser plus alte quando le duo lesiones es presente in combination.

Metieulose studios hemodynamic es un desiderato cardinal in le diagnose de iste lesiones. Le passage del catheter al nivello del ducto establi le diagnose de patentia, e un augmento de plus que 5 pro cento in le saturation oxygenic a ille nivello in comparison con le correspondent valor pro le sanguine dextro-ventricular suggere fortemente que le ducto arteriose es patente. Le grande majoritate del defectos ventriculo-septal esseva diagnosticate per le constatacion de un augmento del saturation oxygenic amontante a 10 pro cento o plus al nivello ventricular. Quasi omne iste patientes habeva hypertension pulmono-arterial.

In 13 patientes, un intervention chirurgic esseva executate. In 9 de istes, solmente le patente ducto arteriose esseva claudite, e in 4 le lesiones esseva

reparate completamente. In le prime de iste 2 gruppos, 2 mortes occurreva, e 2 patientes se meliorava significativamente. In le secunde del 2 gruppos, 2 patientes moriva al chirurgia e 2 esseva marcatamente meliorate. Il pare que iste mortes chirurgie esseva directemente relationate al massive hemorrhagia per le non-suspicite patente ducto arteriose, occurrente quando le circulation (supponitemente) contornava le corde, e al subsequente difficultate technic in le effortio de clauder ambe defectos via un thoracotomia anterior.

Le relation inter le calculate resistentia pulmonovascular e le clausion chirurgie del defectos es discutite.

Es exprime le opinion que si le patente ducto arteriose es diagnosticate super le base de un typic murmure de machineria, le correction de iste lesion es indicate, sin reguardo al associate defecto ventricular. Si, del altere latere, le tableau clinic suggere solamente un defecto ventricular, durante que le presentia del 2 lesiones in combination es discoperite solamente per le catheterismo cardiac, allora le correction simultanee del 2 lesiones es recommendate. In infantes de basse etate, in qui le combine operation es particularmente difficile a iste tempore le essayo preliminar de un regime medical es recommendate. Solmente post que un tal se ha provate van, debe le division del ducto esser effectuate.

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Mitral stenosis may be concealed under a quarter of a dollar. It is the most difficult of all heart disease to diagnose.—SIR WILLIAM OSLER, *Aphorisms From His Bedside Teachings and Writings*. Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 138.

# Atherosclerosis and Related Factors in Immigrants to Israel

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**I**MMIGRANT groups to Israel from western and eastern countries differ widely in morbidity and mortality from coronary disease. They provide, therefore, an opportunity for epidemiologic study of atherosclerosis. The influence of socioeconomic conditions and diet upon blood lipids and proteins was investigated in 2,200 subjects belonging to different immigrant groups and social classes. These findings were correlated with morbidity and mortality rates of the equivalent groups in the whole population.

Atherosclerotic heart disease is recognized in the western world as the chief cause of morbidity and mortality of man at the peak of his mental and social activity. In the search for clues of the etiology of atherosclerosis in man, different workers<sup>1-4</sup> and in particular, Keys,<sup>5</sup> established a positive correlation between the amount of fat in the diet, the level of serum cholesterol, and the frequency of atherosclerosis. Nevertheless, other workers express the opinion that genetic factors might influence the incidence of atherosclerosis.<sup>6,7</sup> Further epidemiologic research is therefore necessary to clarify the effects of the different environmental factors in the pathogenesis of atherosclerosis.

A study of atherosclerosis in different immigrant groups in Israel revealed that its frequency is significantly higher in the groups from western countries than in those from eastern ones. The lowest incidence was found

in the group that had arrived most recently from Yemen.<sup>8-11</sup>

In order to clarify the causes for these differences socioeconomic conditions, diet, and the blood lipids of the various immigrant groups in Israel were examined. The group of immigrants from Yemen, composed of "early" immigrants living in Israel over 20 years and "recent" immigrants living in the country for about 5 years, was of special interest as this genetically pure group made it possible to observe the effect of changing environment on the morbidity and mortality of atherosclerosis.

## Characterization of the Human Material

In 1953 and 1954 we examined the following groups of manual workers: 274 "recent" and 254 "early" Yemenite immigrants,<sup>11</sup> 146 Iraqi immigrants, and 262 European immigrants. In addition, the following groups of immigrants were examined: 400 European white-collar workers, professionals, and middle-class persons and 400 atherosclerotic Europeans with clinically proved myocardial infarction.

In 1957 and 1958 we re-investigated a group of 182 "recent" Yemenites who had by then been resident in Israel for 9 to 10 years (henceforth called "semi-recent") as well as an additional 144 "early" Yemenites and 138 manual workers of European origin (table 1).

All subjects were selected at random and underwent a thorough physical examination by one of us with the help of their local physicians. Persons with a history of cardiovascular disease or other pathology liable to affect the serum cholesterol level were rejected. The following were also rejected: subjects with blood pressure higher than 140/90, subjects

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**Table 1**  
*Distribution of 2,200 Subjects\* (Age 35 to 64)*

Recent Yemenites	Semi-recent Yemenites	Early Yemenites	Iraqi immigrants	Europeans (manual workers)	Europeans (middle class)	Europeans (myocardial infarction)
274	182	398	146	400	400	400

\*Sex and age group distribution is given in table 3.

considerably underweight, subjects with enlargement of the spleen or liver, subjects presenting low blood cholesterol levels in the presence of impaired liver function, and pregnant and lactating women.

#### Social Conditions

The "recent" Yemenites examined in 1953 and 1954 lived in transit camps under poor conditions and were mostly unskilled and partly unemployed manual workers. Their income compared to that of other groups investigated was the lowest (I.L.19.\* per person per month). The economic conditions of the "early" Yemenites examined in 1953 and 1954, who were in the main skilled laborers and farmers, was better with an income of I.L.38. per person per month. In 1957 and 1958 the social conditions of these 2 groups were restudied. Although there was no significant change in the economic conditions of the "early" group, the economic conditions of the "recent" Yemenites was considerably ameliorated. Their monthly income per person had risen to I.L.30.

The income of manual workers of European origin was higher (I.L.68. per person per month) whereas the average income of European white-collar workers, professionals, and middle class reached I.L.90. per person per month.

#### Diet

A dietary survey was conducted in 2 stages by a dietitian with the help of a "recent" Yemenite trained for the purpose. In 1953 and

\*I.L.1.800 = \$1.00

**Table 2**  
*Daily Diet of Different Yemenite Groups in Israel*

	Total calories	Proteins (Gm.)			Fats (Gm.)			% of calories derived from fat
		Animal	Vegetable	Over-all	Animal	Vegetable	Over-all	
Recent Yemenites	1750	12	54	66			30	5
Semi-recent Yemenites	2500	16	70	86	11	54	65	13
Early Yemenites	2535	29	62	91	18	47	65	13

1954, 55 "recent" and 21 "early" Yemenite families were surveyed. In 1957 and 1958, 30 "semi-recent" and 20 "early" Yemenite families were included in the dietary survey. Some of the "semi-recent" Yemenites had formerly belonged to the "recent" group investigated in 1953 and 1954. The daily composition of food of the whole family and the quantity of food consumed by each member of the family was weighed and recorded for 7 consecutive days. The particular method of food preparation as well as types and quantities of spices, which are abundantly in use by these groups, was noted.

The dietary survey of 1953 and 1954 (table 2) showed that the "recent" Yemenites consumed mainly "Pita," a type of flat, yeastless bread; large quantities of vegetables; very little meat (once weekly), and very little fat—mainly in the form of "samne" (boiled butter with "hilbe"\*) . Since the socioeconomic conditions of the "early" Yemenites were better, their caloric intake and the percentage of calories derived from fats were higher than those of the "recent" Yemenites. Both groups made abundant use of sunflower seeds, chickpeas, nuts, and almonds.

The dietary survey of the group of "semi-recent" Yemenites examined in 1957 and 1958 (table 2) revealed that with the improvement in the socioeconomic conditions there was a considerable increase in the total caloric in-

\*The seed of fenugreek, *Trigonella Foenumgræcum* L.

tate as well as in the percentage of calories derived from fats, whereas in "early" Yemenites the increase in total caloric and fat intake was moderate.

#### Clinical and Laboratory Methods

Each subject was weighed and measured nude. Blood pressure was measured in the sitting position; blood samples were collected in the morning from fasting subjects, and the serum was removed 3 to 4 hours later. Every blood examination was performed in duplicate and results diverging by more than 5 per cent were discarded. A detailed description of our methods appeared previously.<sup>10</sup> For the additional determinations of protein,<sup>12</sup> lipoprotein,<sup>13</sup> and cholesterol<sup>14</sup> fractions carried out in 1957 and 1958, paper electrophoretic methods were used. Total blood proteins were determined by a modification of the biuret method. (Globulins were precipitated with solution of sodium sulfate 22.2 per cent.)

#### Results

##### Nutritional Status Expressed by the Weight:Height Ratio (Tables 3 and 4)

###### Men

The lowest weight:height ratio was found among the "recent" Yemenites resident in Israel for about 5 years. After 9 to 10 years residence in Israel, the average weight of the "semi-recent" Yemenites in the age group 45 to 64 increased significantly and reached the weight:height ratio of the "early" Yemenites. The weight:height ratio of the "early" Yemenites approached that of the manual workers of European origin although it was still significantly lower. A significant difference in all age groups was found between middle-class Europeans and European patients with myocardial infarction.

###### Women

The lowest weight:height ratio was found in "recent" and "semi-recent" Yemenites. A significant difference between the "early" Yemenites and "semi-recent" Yemenites remained even after 9 years in Israel. In the 35 to 54 age groups, a higher value of the weight:

height ratio was observed in the middle-class European immigrants than in the manual workers of the same origin. In the age group 45 to 64, the weight:height ratio of the European group with myocardial infarction was significantly higher than that of the middle-class European immigrants.

##### Hemoglobin (Tables 3 and 4)

The mean hemoglobin values in all groups were slightly lower than those accepted in western countries.<sup>15</sup> In women these values were lower than in men for all groups. In men of the 45 to 64 group the hemoglobin values were significantly higher in manual workers of European origin than in "early" Yemenites, whereas in women it was higher in all age groups.

##### Blood Pressure

The lowest mean systolic and diastolic pressures were found in the "recent" Yemenite group. Higher blood pressures were found in the "early" Yemenites, still higher in the Iraqis, increasing with the European manual workers, middle-class, and professional Europeans with myocardial infarction. As cases with elevated blood pressure were excluded from our study, no definite conclusions were drawn from these data.

##### Blood Proteins and Protein Fractions (Table 3)

In general, no significant differences in total proteins, albumin, and globulin fractions were found in any of the groups, regardless of age. A significant difference, however, in albumin, alpha 1 and alpha 2, was found between European manual workers and Europeans with myocardial infarction only in the 55 to 64 age groups.

##### Cholesterol (Tables 3 and 4, Fig. 1)

The mean serum cholesterol value was lowest for "recent" Yemenites examined in 1953 and 1954 in men of all age groups. Values for "early" Yemenites were significantly higher statistically (men:  $t = 7.99 - 6.96 - 7.53$ ; women:  $t = 3.77 - 6.07 - 4.62$ ). Four years later the group of "semi-recent" Yemenites examined showed a significant rise in their

Table 3 Nutritional Status, Blood Lipids, and Proteins of

	Recent Yemenites			Semi-recent Yemenites			Early Yemenites		
	N	M	S.D.	N	M	S.D.	N	M	S.D.
<b>Men age 35-44</b>									
Weight: height ratio*	52	94.5 ± 9.28		23	92.2 ± 3.81		68	100.0 ± 3.33	
Hemoglobin (Gm. %)	52	13.4 ± 0.87		23	13.4 ± 0.46		68	14.2 ± 0.83	
Total cholesterol (mg. %)	52	146.0 ± 28.0		23	151.0 ± 17.54		68	188.0 ± 29.4	
α-Cholesterol (mg. %)				23	39.0 ± 11.8		25	48.0 ± 11.6	
β-Cholesterol (mg. %)				23	112.0 ± 17.8		25	130.0 ± 20.0	
Phospholipids (mg. %)	52	207.3 ± 22.7					68	210.3 ± 19.1	
α-Phospholipids (mg. %)				23	50.0 ± 5.53		25	47.0 ± 5.2	
β-Phospholipids (mg. %)				23	50.0 ± 5.53		25	53.0 ± 5.2	
Cholesterol: phospholipid ratio	52	0.72 ± 0.15					43	0.88 ± 0.1	
α-Lipoproteins (%)				23	26.5 ± 6.49		25	27.3 ± 5.9	
β-Lipoproteins (%)				23	73.5 ± 6.49		25	72.7 ± 5.9	
Total lipids (mg. %)	52	556.3 ± 67.4					43	634.0 ± 111.0	
Total proteins (Gm. %)				23	6.8 ± 0.52		25	6.8 ± 0.41	
Protein fractions (%)									
Albumin				23	55.4 ± 6.07		25	55.7 ± 3.47	
α <sub>1</sub>				23	4.2 ± 1.24		25	4.4 ± 1.18	
α <sub>2</sub>				23	8.3 ± 2.61		25	9.1 ± 2.22	
β				23	10.9 ± 1.98		25	11.4 ± 2.44	
γ				23	21.2 ± 3.83		25	19.4 ± 2.99	
<b>Men age 45-54</b>									
Weight: height ratio*	57	92.4 ± 8.2		53	97.5 ± 5.12		72	96.0 ± 8.58	
Hemoglobin (Gm. %)	57	13.6 ± 0.57		53	13.6 ± 0.41		72	14.0 ± 0.76	
Total cholesterol (mg. %)	57	158.0 ± 31.7		53	180.0 ± 21.9		72	197.0 ± 32.9	
α-Cholesterol (mg. %)				23	42.0 ± 8.7		24	44.0 ± 11.6	
β-Cholesterol (mg. %)				23	130.0 ± 15.4		24	149.0 ± 25.5	
Phospholipids (mg. %)	57	212.0 ± 52.1					72	229.0 ± 37.5	
α-Phospholipids (mg. %)				23	48.3 ± 6.19		24	45.3 ± 7.1	
β-Phospholipids (mg. %)				23	51.7 ± 6.19		24	54.7 ± 7.1	
Cholesterol: phospholipid ratio	57	0.76 ± 0.14					72	0.87 ± 0.12	
α-Lipoproteins (%)				23	25.2 ± 6.2		24	22.8 ± 5.0	
β-Lipoproteins (%)				23	74.8 ± 6.2		24	77.2 ± 5.0	
Total lipids (mg. %)	57	607.0 ± 105.3							
Total proteins (Gm. %)				23	7.1 ± 0.58		24	6.8 ± 0.46	
Protein fractions (%)									
Albumin				23	54.0 ± 5.39		24	56.2 ± 3.25	
α <sub>1</sub>				23	4.4 ± 1.07		24	4.3 ± 0.83	
α <sub>2</sub>				23	8.8 ± 1.55		24	8.8 ± 1.82	
β				23	11.6 ± 2.08		24	11.9 ± 1.35	
γ				23	21.2 ± 4.17		24	18.8 ± 3.23	
<b>Men age 55-64</b>									
Weight: height ratio*	56	86.8 ± 9.8		51	94.2 ± 6.4		62	93.1 ± 8.43	
Hemoglobin (Gm. %)	56	12.9 ± 0.82		51	13.0 ± 0.43		62	13.3 ± 0.98	
Total cholesterol (mg. %)	56	158.0 ± 28.7		51	188.0 ± 19.7		62	205.0 ± 38.4	
α-Cholesterol (mg. %)				19	44.0 ± 13.2		25	43.0 ± 11.8	
β-Cholesterol (mg. %)				19	137.0 ± 20.3		25	160.0 ± 34.5	
Phospholipids (mg. %)	56	205.0 ± 48.0					62	229.0 ± 46.9	
α-Phospholipids (mg. %)				19	51.1 ± 6.25		25	45.5 ± 6.6	
β-Phospholipids (mg. %)				19	48.9 ± 6.25		25	54.5 ± 6.6	
Cholesterol: phospholipid ratio	56	0.79 ± 0.12					62	0.9 ± 0.17	
α-Lipoproteins (%)				19	27.3 ± 6.54		25	21.5 ± 5.75	
β-Lipoproteins (%)				19	72.7 ± 6.54		25	78.5 ± 5.75	
Total lipids (mg. %)	56	594.0 ± 92.8					37	655.0 ± 101.0	
Total proteins (Gm. %)				19	6.8 ± 0.45		25	6.9 ± 0.57	
Protein fractions (%)									
Albumin				19	55.3 ± 5.38		25	56.2 ± 3.97	
α <sub>1</sub>				19	4.8 ± 0.83		25	4.3 ± 0.93	
α <sub>2</sub>				19	9.6 ± 2.76		25	9.0 ± 1.22	
β				19	11.1 ± 1.12		25	11.6 ± 1.34	
γ				19	19.2 ± 3.19		25	18.9 ± 3.57	

## 2200 Subjects of Different Immigrant Groups in Israel

Iraqis			European manual workers			European middle class			Europeans with myocardial infarction		
N	M	S.D.	N	M	S.D.	N	M	S.D.	N	M	S.D.
1	100.4 ± 5.55		88	104.0 ± 7.4		76	102.0 ± 2.7		73	107.7 ± 7.8	
1	13.6 ± 0.41		88	14.5 ± 0.7		76	14.7 ± 0.7		73	14.3 ± 0.7	
1	195.7 ± 20.08		88	186.0 ± 27.8		76	210.0 ± 34.6		73	252.0 ± 35.0	
			34	39.0 ± 11.6					29	37.0 ± 10.6	
			34	153.0 ± 30.8					29	201.0 ± 32.2	
1	240.6 ± 24.9		42	228.0 ± 25.3					29	216.0 ± 27.2	
			34	44.4 ± 6.7					29	38.7 ± 7.0	
			34	55.6 ± 6.7					29	61.3 ± 7.0	
1	0.82 ± 0.04		42	0.79 ± 0.05					29	1.12 ± 0.04	
			34	21.4 ± 6.3					29	16.4 ± 4.7	
			34	78.6 ± 6.3					29	83.6 ± 4.7	
1	650.0 ± 58.0		42	614.0 ± 72.1							
			34	6.7 ± 0.43					29	6.7 ± 0.7	
			34	56.0 ± 5.7					29	56.2 ± 4.0	
			34	4.4 ± 1.3					29	4.1 ± 0.98	
			34	10.1 ± 2.9					29	11.5 ± 3.4	
			34	11.5 ± 1.5					29	11.5 ± 2.0	
			34	18.0 ± 2.5					29	16.7 ± 2.2	
24	102.0 ± 6.7		97	102.0 ± 8.7		79	103.0 ± 4.0		117	106.5 ± 8.8	
24	13.7 ± 0.84		97	14.4 ± 0.6		79	15.1 ± 0.4		117	14.5 ± 0.5	
24	201.0 ± 19.4		97	190.0 ± 25.8		79	248.0 ± 28.2		117	251.0 ± 41.0	
			40	39.0 ± 11.0					45	42.0 ± 14.7	
			40	151.0 ± 24.0					44	205.0 ± 38.9	
24	244.0 ± 27.9		51	233.0 ± 28.1					44	233.0 ± 40.5	
			40	44.9 ± 6.5					44	40.0 ± 6.5	
			40	55.1 ± 6.5					44	60.0 ± 6.5	
24	0.83 ± 0.03		51	0.80 ± 0.04					44	1.05 ± 0.03	
			40	22.0 ± 6.1					44	15.0 ± 4.8	
			40	78.0 ± 6.1					44	85.0 ± 4.8	
24	676.0 ± 55.6		51	634.0 ± 87.2							
			40	6.7 ± 0.48					44	6.9 ± 0.4	
			40	58.1 ± 5.23					44	58.0 ± 5.1	
			40	4.1 ± 1.03					44	4.0 ± 1.1	
			40	9.5 ± 2.27					44	10.0 ± 2.6	
			40	11.2 ± 1.64					44	11.0 ± 1.8	
			40	17.1 ± 3.06					44	17.0 ± 2.4	
21	95.6 ± 7.1		91	103.0 ± 6.9		62	104.0 ± 4.2		121	107.4 ± 10.9	
21	12.9 ± 0.9		91	14.2 ± 0.7		62	14.8 ± 0.5		121	14.4 ± 0.5	
21	198.0 ± 24.2		91	203.0 ± 30.6		62	239.0 ± 34.6		121	254.0 ± 55.2	
			36	40.0 ± 13.3					44	41.0 ± 12.8	
			36	172.0 ± 30.4					44	199.0 ± 46.7	
21	241.0 ± 28.3		45	223.0 ± 44.4					44	224.0 ± 40.6	
			36	42.0 ± 7.9					44	43.5 ± 7.2	
			36	58.0 ± 7.9					44	56.5 ± 7.2	
2	0.83 ± 0.04		45	0.80 ± 0.05					44	1.08 ± 0.11	
			36	19.1 ± 5.7					44	16.5 ± 5.4	
			36	80.9 ± 5.7					44	83.5 ± 5.4	
2	677.0 ± 59.6		45	654.0 ± 113.0							
			36	6.7 ± 0.5					44	6.6 ± 0.5	
			36	57.2 ± 4.7					44	54.0 ± 6.1	
			36	3.9 ± 0.3					44	5.2 ± 1.7	
			36	9.7 ± 2.3					44	11.7 ± 3.1	
			36	11.5 ± 1.7					44	11.6 ± 1.4	
			36	17.7 ± 2.5					44	17.5 ± 2.9	

Table 3 Nutritional Status, Blood Lipids, and Proteins of 2,20

	Recent Yemenites			Semi-recent Yemenites			Early Yemenites		
	N	M	S.D.	N	M	S.D.	N	M	S.D.
<b>Women age 35-44</b>									
Weight: height ratio*	42	93.6 ± 8.05		15	92.0 ± 2.14		75	101.0 ± 34.9	
Hemoglobin (Gm. %)	42	12.5 ± 0.99		15	12.3 ± 0.34		75	12.3 ± 0.9	
Total cholesterol (mg. %)	42	172.0 ± 25.9		15	183.0 ± 20.2		75	193.0 ± 21.8	
α-Cholesterol (mg. %)				15	40.9 ± 14.9		28	46.0 ± 11.3	
β-Cholesterol (mg. %)				15	139.7 ± 20.9		28	148.0 ± 24.2	
Phospholipids (mg. %)	42	237.0 ± 46.6					47	228.0 ± 37.0	
α-Phospholipids (mg. %)				15	46.7 ± 5.59				
β-Phospholipids (mg. %)				15	53.3 ± 5.59				
Cholesterol: phospholipid ratio	42	0.75 ± 0.12					47	0.86 ± 0.11	
α-Lipoproteins (%)				15	24.3 ± 6.38				
β-Lipoproteins (%)				15	75.7 ± 6.38				
Total lipids (mg. %)	42	618.0 ± 71.7					47	664.0 ± 82.9	
Total proteins (Gm. %)				15	7.1 ± 0.38		28	6.8 ± 0.48	
Protein fractions (%)									
Albumin				15	57.2 ± 3.99		28	55.3 ± 3.65	
α <sub>1</sub>				15	3.9 ± 1.15		28	4.6 ± 1.26	
α <sub>2</sub>				15	8.0 ± 1.75		28	9.1 ± 2.21	
β				15	10.9 ± 1.21		28	11.6 ± 1.25	
γ				15	20.0 ± 2.58		28	19.4 ± 3.21	
<b>Women age 45-54</b>									
Weight: height ratio*	43	94.6 ± 9.76		22	94.0 ± 4.18		76	108.0 ± 16.05	
Hemoglobin (Gm. %)	43	12.3 ± 0.76		22	11.9 ± 0.49		76	12.4 ± 0.89	
Total cholesterol (mg. %)	43	172.0 ± 28.8		22	189.0 ± 20.1		76	206.0 ± 30.5	
α-Cholesterol (mg. %)				22	43.8 ± 9.5		22	44.0 ± 11.02	
β-Cholesterol (mg. %)				22	150.4 ± 18.4		22	157.0 ± 37.6	
Phospholipids (mg. %)	43	219.0 ± 39.2					76	236.0 ± 30.2	
α-Phospholipids (mg. %)				17	46.7 ± 6.46		22	46.5 ± 6.9	
β-Phospholipids (mg. %)				17	53.3 ± 6.46		22	53.5 ± 6.9	
Cholesterol: phospholipid ratio	43	0.80 ± 0.12					54	0.88 ± 0.11	
α-Lipoproteins (%)				17	23.0 ± 4.42		22	23.1 ± 5.3	
β-Lipoproteins (%)				17	77.0 ± 4.42		22	76.9 ± 5.3	
Total lipids (mg. %)	43	615.0 ± 89.5					54	694.0 ± 97.1	
Total proteins (Gm. %)				17	6.9 ± 0.63		22	6.9 ± 0.4	
Protein fractions (%)									
Albumin				17	54.4 ± 3.97		22	56.7 ± 4.45	
α <sub>1</sub>				17	4.6 ± 1.13		22	4.6 ± 0.87	
α <sub>2</sub>				17	9.7 ± 2.4		22	8.8 ± 1.55	
β				17	11.7 ± 1.83		22	11.0 ± 1.36	
γ				17	19.6 ± 3.68		22	18.9 ± 3.56	
<b>Women age 55-64</b>									
Weight: height ratio*	24	94.9 ± 11.2		18	94.0 ± 5.33		45	108.6 ± 15.1	
Hemoglobin (Gm. %)	24	12.3 ± 0.78		18	12.0 ± 0.54		45	12.5 ± 0.94	
Total cholesterol (mg. %)	24	190.0 ± 26.3		18	183.0 ± 26.8		45	224.0 ± 34.1	
α-Cholesterol (mg. %)				18	49.6 ± 16.7		20	45.0 ± 14.4	
β-Cholesterol (mg. %)				18	138.8 ± 25.1		20	173.0 ± 29.1	
Phospholipids (mg. %)	24	233.0 ± 36.8					45	246.0 ± 31.9	
α-Phospholipids (mg. %)							20	45.0 ± 5.9	
β-Phospholipids (mg. %)							20	55.0 ± 5.9	
Cholesterol: phospholipid ratio	24	0.83 ± 0.11					25	0.94 ± 0.13	
α-Lipoproteins (%)							20	22.8 ± 7.7	
β-Lipoproteins (%)							20	77.2 ± 7.7	
Total lipids (mg. %)	24	633.0 ± 65.1					25	722.0 ± 97.3	

N, number; M, mean; S.D., standard deviation.

\* Weight (Kg.)

× 100.  
Height (cm.) - 100

## Subjects of Different Immigrant Groups in Israel (Continued)

Iraqis			European manual workers			European middle class			Europeans with myocardial infarction		
N	M	S.D.	N	M	S.D.	N	M	S.D.	N	M	S.D.
38	99.7 ± 8.78		37	98.8 ± 12.02		72	107.0 ± 3.42				
38	12.2 ± 0.63		37	13.4 ± 0.68		72	13.5 ± 0.76				
38	197.0 ± 25.7		37	185.7 ± 22.7		72	221.0 ± 31.4				
38	238.5 ± 28.5		37	232.0 ± 26.4							
38	0.82 ± 0.05		37	0.80 ± 0.05							
38	646.0 ± 79.8		37	626.0 ± 75.9							
24	99.8 ± 10.0		55	99.8 ± 10.02		55	108.0 ± 4.77		45	114.5 ± 7.89	
24	12.0 ± 0.6		55	12.0 ± 0.61		55	13.0 ± 0.49		45	13.0 ± 0.67	
24	205.0 ± 18.8		55	205.0 ± 18.8		55	228.0 ± 25.9		45	262.0 ± 44.3	
24	251.0 ± 27.1		55	251.0 ± 27.1							
24	0.82 ± 0.03		55	0.81 ± 0.05							
24	683.0 ± 68.4		55	683.0 ± 68.4							
28	101.5 ± 19.9		32	108.0 ± 11.2		56	105.0 ± 4.78		48	113 ± 11.5	
28	12.2 ± 0.2		32	13.2 ± 0.74		56	12.5 ± 0.82		44	12.5 ± 0.51	
28	203.0 ± 20.9		32	207.0 ± 35.1		56	244.0 ± 30.65		44	260.0 ± 46.7	
28	245.0 ± 27.2		32	256.0 ± 38.8							
28	0.83 ± 0.04		32	0.81 ± 0.05							
32	681.0 ± 82.4		32	674.0 ± 112.0							

Table 4—Comparison of Nutritional Status and Blood Lipid Values in

	Semi-recent Yemenites vs. recent Yemenites	Early Yemenites vs. semi-recent Yemenites	Early Yemenites vs. recent Yemenites	Iraqis vs. early Yemenites	European manual workers vs. early Yemenites	European manual workers vs. European middle class	Europeans with myocardial infarction vs. European middle class
Men age 35—44							
Weight: height ratio	NS*	++†	++	NS	+	NS	++
Hemoglobin	NS	++	++	++	NS	NS	++
Total cholesterol	NS	+	++	NS	NS	++	++
α-Cholesterol		+			+		
β-Cholesterol		+			+		
Phospholipids	++	++	NS	+	NS		
Cholesterol: phospholipids ratio	NS	NS	++	+	++		
α-Lipoproteins		NS			+		
β-Lipoproteins		NS			+		
Men age 45—54							
Weight: height ratio	++	NS	+	++	++	NS	++
Hemoglobin	NS	NS	+	NS	++	++	++
Total cholesterol	++	++	++	NS	NS	++	NS
α-Cholesterol		NS			NS		
β-Cholesterol		++			NS		
Phospholipids	NS	++	NS	NS	NS		
Cholesterol: phospholipid ratio	++	+	+	NS	NS		
α-Lipoproteins		NS			NS		
β-Lipoproteins		NS			NS		
Men age 55—64							
Weight: height ratio	++	NS	++	NS	++	NS	+
Hemoglobin	NS	NS	NS	NS	++	++	++
Total cholesterol	++	+	++	NS	NS	++	+
α-Cholesterol		NS			NS		
β-Cholesterol		+			NS		
Phospholipids	NS	+	+	NS	NS		
Cholesterol: phospholipid ratio	++	NS	+	+	+		
α-Lipoproteins		+			NS		
β-Lipoproteins		+			NS		

mean cholesterol values—for men in the 45 to 54 and 55 to 64 age groups ( $t = 4.23$  to  $6.21$ ) and women in the 45 to 54 age group ( $t = 2.7$ ). These values, however, were still significantly lower than the mean cholesterol values of the "early" Yemenites in men of all age groups.

There was no significant difference in the mean serum cholesterol values among the "early" Yemenites, the Iraqi, and European manual workers. A highly significant difference was found between the European manual

workers and the European middle class in both sexes and in all age groups (men:  $t = 4.85 - 14.1 - 8.13$ ; women:  $t = 5.77 - 5.3 - 5.05$ ). The highest cholesterol values were found in the group of European patients with myocardial infarction.

**Alpha and Beta Cholesterol (Tables 3 and 4, Figs. 1 and 2)**

Comparison of "semi-recent" Yemenites and "early" Yemenites showed a significant increase in beta cholesterol values in milligrams per cent for "early" Yemenite men 35

## Immigrant Groups in Israel (Comparison Is Based on the Test of Significance)

	Semi-recent Yemenites vs. recent Yemenites	Early Yemenites vs. semi-recent Yemenites	Early Yemenites vs. recent Yemenites	Iruels vs. early Yemenites	European manual workers vs. early Yemenites	European manual workers vs. European middle class	Europeans with myocardial infarction vs. European middle class
<b>Women age 35—44</b>							
Weight: height ratio	NS	++	++	NS	NS	++	
Hemoglobin	NS	NS	NS	NS	++	NS	
Total cholesterol	NS	NS	++	NS	NS	++	
α-Cholesterol		NS					
β-Cholesterol		NS					
Phospholipids	++	++	NS	NS	NS		
Cholesterol: phospholipid ratio	++	++	+	NS	NS		
α-Lipoproteins							
β-Lipoproteins							
<b>Women age 45—54</b>							
Weight: height ratio	NS	++	++	+	++	++	++
Hemoglobin	+	+	NS	NS	+	++	NS
Total cholesterol	+	NS	++	NS	NS	++	++
α-Cholesterol		NS					
β-Cholesterol		NS					
Phospholipids	NS	++	+	NS	NS		
Cholesterol: phospholipid ratio	++	NS	+	+	++		
α-Lipoproteins							
β-Lipoproteins							
<b>Women age 55—64</b>							
Weight: height ratio	NS	++	++	+	NS	NS	++
Hemoglobin	NS	+	NS	NS	++	++	NS
Total cholesterol	NS	++	++	+	NS	++	NS
α-Cholesterol		NS					
β-Cholesterol		++					
Phospholipids	+	++	NS	NS	NS		
Cholesterol: phospholipids ratio	NS	NS	NS	+	++		
α-Lipoproteins							
β-Lipoproteins							

\*NS, nonsignificant.

†++, highly significant: critical ratio &gt;3.5.

‡+, significant: critical ratio &gt;2.5.

to 64 years old ( $t = 2.57, 3.4, 2.7$ ) and women 55 to 64 years old ( $t = 3.86$ ). A highly significant difference in beta cholesterol was found between European manual workers and men with myocardial infarction of all 3 age groups ( $t = 6.02, 7.87, 3.11$ ). No significant difference was found in alpha cholesterol between these 2 groups.

The outstanding results were the constancy of alpha cholesterol in milligrams per cent

and the variability of beta cholesterol in all groups examined (fig. 2).

**Lipoproteins (Tables 3 and 4)**

Comparison between "semi-recent" Yemenites and "early" Yemenites showed significantly lower alpha lipoprotein and higher beta lipoprotein values in men 55 to 64 years old. Significantly higher values for beta lipoproteins were found in European men, manual workers, 35 to 44 years old ( $t = 3.37$ ).

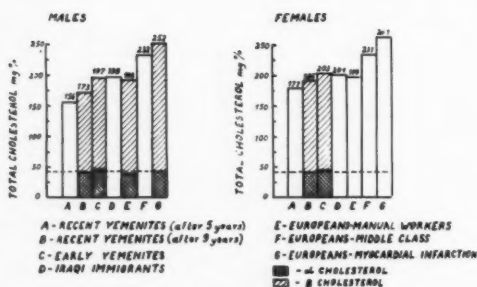


Figure 1

Total alpha and beta cholesterol in different ethnic and social groups in Israel. Age 35 to 64.

#### Phospholipids (Tables 3 and 4)

Significant differences in phospholipid values were found between "recent" Yemenites and "semi-recent" Yemenites between men 35 to 44 and women 35 to 44 and 55 to 64 years old. A comparison between the "semi-recent" and "early" Yemenites showed significant difference in all age groups of both sexes.

#### Cholesterol:Phospholipid Ratio (Tables 3 and 4)

The cholesterol:phospholipid ratio followed the general pattern of differences in cholesterol levels among the various groups.

#### Morbidity from Myocardial Infarction

In order to evaluate the incidence of morbidity from atherosclerosis in the different groups, we reviewed 5,000 cases of myocardial infarction from all but one of the leading hospitals in Israel over the period 1947 to 1957. On the basis of this material we calculated the incidence of myocardial infarction in "early" and "recent" Yemenites and eastern and western immigrants (fig. 3). The relative difference in morbidity from myocardial infarction in the various groups is expressed as rates per 1,000 persons of the same sex and age group in the whole population. The respective rates were *men*: "recent" Yemenites, 0.1; "early" Yemenites, 1.6; immigrants of eastern origin, 5.2; immigrants of western origin, 17.7; *women*: "recent" Yemenites, 0; "early" Yemenites, 0.2; immigrants of eastern origin, 1.4; immigrants of western origin, 4.4. It is to

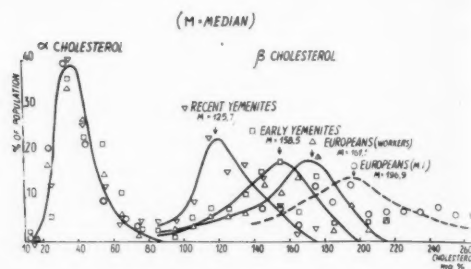


Figure 2

Distribution of alpha and beta cholesterol values in Yemenite and European immigrants to Israel.

be stressed that members of all immigrant groups had the same access to all hospitals concerned.

#### Mortality Rates from Atherosclerosis

Data concerning atherosclerosis mortality rates for the various immigrant groups covering the period 1953 to 1957 for the whole population of Israel are presented in table 5.

The atherosclerotic mortality rate for 1953 to 1957 of the "early" Yemenites in the 45 to 64 age group was about 4 times the mortality rate of "recent" Yemenites in men and 3 times in women. The mortality rate of the European Jews was considerably higher.

The mortality from all other diseases in men of both Yemenite groups is practically the same (table 6).

As mentioned elsewhere,<sup>11</sup> these figures were based on clinical rather than on postmortem examination, but since most of the population, and practically all of the eastern immigrants, get their medical treatment through the Sick Fund of the General Federation of Labour, the proportion of errors due to death certificates based on clinical diagnosis is likely to be the same in the different groups.

#### Coronary Atherosclerosis and Myocardial Infarction

In order to obtain a quantitative correlation between the extent of coronary atherosclerosis and myocardial infarction, we summarized the results of 385 postmortem examinations performed in our hospital on patients who had died of myocardial infarction (table 7). In

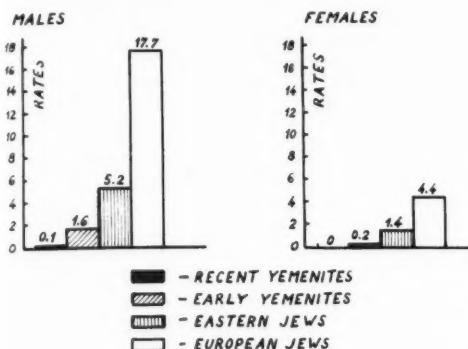


Figure 3

Incidence of myocardial infarction (rates per 1,000 inhabitants) based on 5,000 hospitalized cases 1947-1957.

about 80 per cent of the autopsies performed, severe atherosclerotic changes in the coronary arteries were found; in the other 20 per cent moderate atherosclerotic changes were observed.

#### Serum Cholesterol and Mortality from Atherosclerosis

Comparison of serum cholesterol levels and mortality rates from atherosclerosis (fig. 4) shows that the "recent" Yemenites with the lowest serum cholesterol values also have the lowest mortality rates from atherosclerosis; the "early" Yemenites with higher cholesterol values have a higher mortality rate from atherosclerosis.

#### Discussion

This epidemiologic study shows that atherosclerosis was lowest in the group of "recent" immigrants from Yemen, the poorest among the groups investigated. In 1953 and 1954, after 5 years in Israel, their nutritional status and blood cholesterol levels were lower than that of any other group of Israeli inhabitants.

A follow-up study of this group in 1957 and 1958, after 9 to 10 years in Israel, showed that their socioeconomic condition had improved and that there was a rise of 43 per cent in their total caloric intake as well as a rise of 7 per cent in their percentage of calories derived from fats (table 2). In men

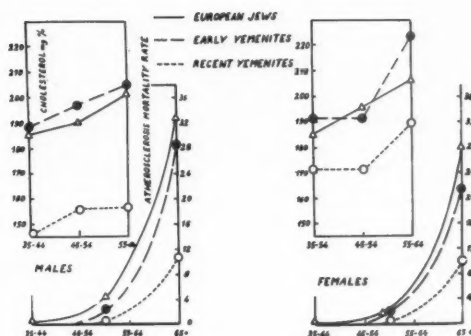


Figure 4

Mortality from atherosclerosis and cholesterol values in European, early and recent Yemenite immigrants to Israel 1953-1957.

45 to 64 years old there was a highly significant increase in their nutritional status as well as in serum cholesterol level. These findings demonstrate the gradual transition of the poorest group of "recent" Yemenites with the lowest cholesterol level to the economically better-off group of "early" Yemenites with higher cholesterol levels.

Dietary survey of the "early" Yemenites showed that although the composition of their food remained essentially similar to that of the "recent" Yemenites, their total caloric and fat intake increased and approached that of the European manual workers.<sup>16</sup>

It can be assumed that the rise in serum cholesterol level in the "semi-recent" and "early" Yemenites is due to over-all higher caloric and fat intake. Another factor to be considered is a possible change in the ratio of saturated to unsaturated fatty acids<sup>2, 17-20</sup> or a shift to a less bulky diet poorer in vegetables. These possibilities are now under investigation.

The morbidity and mortality from atherosclerosis of the "early" Yemenites is higher than that of the "recent" Yemenites, but the mortality from other diseases is practically the same in both groups. As the "recent" and "early" Yemenites belong to the same genetic group, the difference in their serum cholesterol values can be mainly attributed to the differ-

Table 5

*Mortality from Atherosclerosis in European and Yemenite Immigrants to Israel (Average for 1955 to 1957. Rates per 1,000 Inhabitants)*

	Age	European immigrants		Yemenite immigrants		Recent	
		No.	Rates	No.	Rates	No.	Rates
Men	35-44	39	0.48	—	—	—	—
	45-64	530	4.68	5	2.5	2	0.6
Women	35-44	15	0.18	—	—	—	—
	45-64	200	2.00	4	2.3	3	0.8

ences in diet consequent to changing socioeconomic conditions. This increase in serum cholesterol values in "early" Yemenites may cause the increase in the morbidity and mortality from atherosclerosis.

Another indication that the caloric imbalance is an important factor in determining the group incidence of atherosclerosis is that during World War I and particularly World War II, when food was scanty, the over-all mortality from atherosclerosis was considerably diminished.<sup>21-24</sup> Likewise, physicians who survived the Nazi concentration camps reported that during the years of their imprisonment, they never encountered patients with myocardial infarctions or patients with anginal syndrome, even in persons over 50 years of age. Moreover, persons who were previously known to them as patients with atherosclerotic heart disease became free of clinical manifestations of their disease after losing considerable weight due to the conditions prevailing in the concentration camps.<sup>25-27</sup>

#### Cholesterol as an Atherogenic Index

Comparison of the incidence of atherosclerosis with the results of clinical and laboratory investigations shows that only the total and beta cholesterol levels give a direct correlation with the epidemiologic data. Neither the other blood lipids nor the protein fractions show any significant differences among the various groups examined.

As the alpha cholesterol was found to be constant in both sexes and all ages of the various population groups while the variability was localized in the beta cholesterol,

Table 6

*Mortality from Cardiovascular Diseases and All Other Causes in European and Yemenite Immigrants to Israel (Average for 1955 to 1957. Rates per 1,000 Inhabitants)*

	Age	European immigrants		Yemenite immigrants		Recent	
		Cardiovascular disease	Other causes	Cardiovascular disease	Other causes	Cardiovascular disease	Other causes
Men	45-64	5.3	3.7	1.9	4.2	0.9	4.5
Women	45-64	2.0	4.7	1.3	3.5	1.2	5.8

determination of total cholesterol alone can serve as an atherogenic index.

In the different population groups examined, it was found that an improvement in the socioeconomic status is accompanied by an increase in the cholesterol content of the blood. It can, consequently, be stated that the mean cholesterol level is a socioeconomic characteristic of a population group and can be allotted varying values for different social groups of the same age, sex, and ethnic origin. This fact is seen not only among the Yemenites but also among the various classes of western immigrants (fig. 1). This corresponds to similar findings in different social classes in Spain,<sup>28</sup> Italy,<sup>29</sup> and India<sup>30</sup> as well as in Japanese in Japan and Japanese in Hawaii.<sup>31</sup> The so-called cholesterol norms of the western or westernized countries are "simply standards for preclinical coronary disease,"<sup>31</sup> as pointed out by Keys, and should be substituted by a mean value obtained from population groups nearly free of atherosclerosis found in underdeveloped countries.

On the basis of our available data, it seems that the value of a normal cholesterol level in adults is about 160 mg. per cent in men and 180 mg. per cent in women, as found in "recent" Yemenites. These values were also confirmed by other workers.<sup>32</sup>

The cholesterol level of blood withdrawn from the umbilical cord of newborn infants of different population groups throughout the

Table 7

Condition of Coronary Arteries Found on Autopsy of 385 Cases of Myocardial Infarction (Age 43-77)

Coronary arteries	Men		Women	
	No.	Per cent	No.	Per cent
Severe atherosclerosis	226	79.9	85	83.3
Moderate atherosclerosis	57	20.1	17	16.7

world showed no dissimilarity due to race or class and, in almost all cases, was about 80 mg. per cent.<sup>33-35</sup> The rise of cholesterol occurs at an early age and is dependent upon the composition of diet.<sup>35</sup>

#### Prevention of Atherosclerosis

Since myocardial infarction is the main cause of morbidity and mortality in western civilization, its prevention is a major problem of public health. Although multiple factors, such as changes in blood coagulability, physical activity, stress, and hormones as well as local factors in the coronary arteries are implicated in the pathogenesis of myocardial infarction, atherosclerosis is generally accepted as being its underlying cause. In our material (table 7), no case of myocardial infarction without atherosclerosis was found, and about 80 per cent of the cases had severe coronary atherosclerosis. The present observations on 2,200 subjects of western and eastern origin and of different socioeconomic groups corroborate the investigations carried out in underdeveloped countries which show that, in populations with low serum cholesterol values, the mortality rate from myocardial infarction is correspondingly low.<sup>2, 36-38</sup> With amelioration of the socioeconomic status, along with an increase in the total caloric intake, a decrease in consumption of bulky vegetable food and an increase in percentage of calories derived from fats, blood cholesterol and atherosclerotic mortality rate rises. These observations suggest that the appearance of atherosclerosis in any population group may be retarded or prevented by maintaining a balanced caloric intake of a bulky diet with no more than 15 to 20 per cent of calories derived from fats.

#### Summary

Clinical experience in Israel, supported by statistical surveys, showed a low incidence of atherosclerosis among immigrants from eastern countries as compared to immigrants from western countries. In particular, the incidence of atherosclerosis among immigrants from Yemen was found to be strikingly low.

An investigation of the socioeconomic condition, diet, and nutritional status of 2,200 immigrants from western and eastern countries belonging to different social groups was carried out. Determinations of serum total lipids, total cholesterol, alpha and beta cholesterol, phospholipids, lipoproteins, proteins, and protein fractions were performed.

Significantly the lowest serum cholesterol and beta cholesterol values were found among the "recent" Yemenites (after 5 years in Israel), the poorest economically, and with an imbalanced caloric intake of the lowest fat content. Higher cholesterol and beta cholesterol values were found among "early" (after 20 years in Israel) Yemenites, Iraqi, and European manual workers with no significant differences among them, whereas in Europeans of higher economic level these values were even higher.

Review of 5,000 hospitalized cases of myocardial infarction showed a very low incidence for Yemenites, higher for immigrants from other eastern countries, and considerably higher for European immigrants.

A statistical survey of the entire population for the years 1953 to 1957 showed that the mortality rate from atherosclerosis was extremely low for "recent" Yemenites, considerably higher for "early" Yemenites, and still higher for European immigrants.

These results suggest the influence of socioeconomic conditions, diet, and total caloric balance on serum cholesterol values and atherosclerosis morbidity and mortality. They support the assumption that atherosclerosis is a disease of lipid metabolism influenced by phenotypic factors and therefore can be prevented.

### Acknowledgment

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### Summario in Interlingua

Experientias clinic in Israel, supportate per evidencia statistic, indica un basse incidentia de atherosclerosis inter le immigrantes ab pais al est in comparison con illo inter immigrantes ab pais al west. Particularmente, le incidentia de atherosclerosis inter le immigrantes ab Yemen se monstrava como frappantemente basse.

Esseva effectuate un investigation del condition socio-economic, del dieta, e del stato nutritional de 2.200 immigrantes ab le est e le west e ab diverse gruppos social. Esseva executate determinaciones del lipidos total del sero, del cholesterol total, del cholesterol alpha e beta, de phospholipidos, de lipoproteinas, de proteinas, e de fractiones de proteina.

Significativamente le plus basse valores seral de cholesterol e cholesterol beta esseva trovate inter le recente yemenitas (in Israel deposite 5 annos), qui es economicamente le plus povre e qui ha un mal balanciate ingestion calorie con le plus basse contento de grassia. Plus alte valores de cholesterol e cholesterol beta esseva trovate inter yemenitas precoce (in Israel deposite 20 annos), iraqi, e europees obreros manual. Inter iste gruppos nulle significative differentias esseva constatate, sed in europeos de plus elevate nivellos economic, le valores esseva ancora plus alte.

Un revista de 5.000 hospitalisate casos de infarctamento myocardial revelava un bassissime incidentia pro yemenitas; iste incidentia esseva plus alte pro immigrantes ab le pais del est e considerabilemente plus alte pro le immigrantes europees.

Un studio statistic del integre population pro le annos ab 1953 a 1957 monstrava que le mortalitate ab atherosclerosis esseva extrememente basse pro recente yemenitas, considerabilemente plus alte pro yemenitas precoce, e ancora plus alte pro immigrantes europees.

Iste resultados signala un influentia del conditiones socio-economic, del dieta, e del balancia calorie total super le valores del cholesterol seral e super le morbiditate e mortalitate ab atherosclerosis. Illos supporta le supposition que atherosclerosis es un morbo

del metabolismo lipidic que pote esser prevenite ben que illo es influentiate per factores phenotypic.

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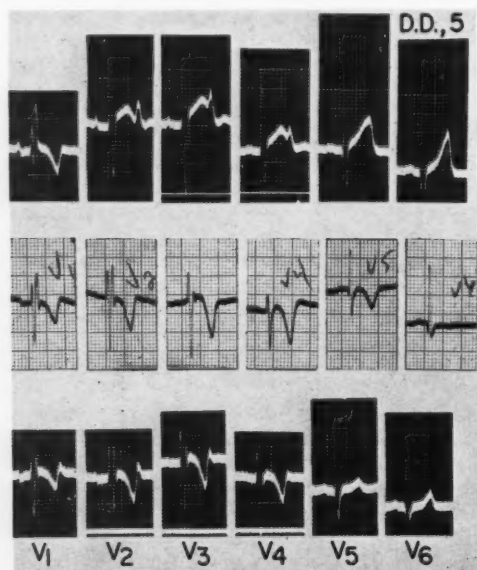
# Electrocardiographic Sequelae of Right Ventriculotomy in Patients with Ventricular Septal Defects

By JUNE M. FISHER, M.D., ERNEST O. THEILEN, M.D., LEWIS E. JANUARY, M.D.,  
AND JOHANN L. EHRENHAFT, M.D.

**M**OST of the children operated on for the repair of ventricular septal defects recuperate with surprising rapidity, and the morbidity associated with the surgery is low. Many of the children have essentially normal hearts on both physical and radiographic examination after the immediate postoperative period. In general they seem to thrive. This state does not mean that open-heart sur-

gery may not sometimes produce myocardial changes which are not apparent immediately. We have observed persistent electrocardiographic changes after ventriculotomy that suggest damage to the myocardium even though the patient may be well clinically. It is still too early to evaluate fully the clinical significance of some of the abnormalities.

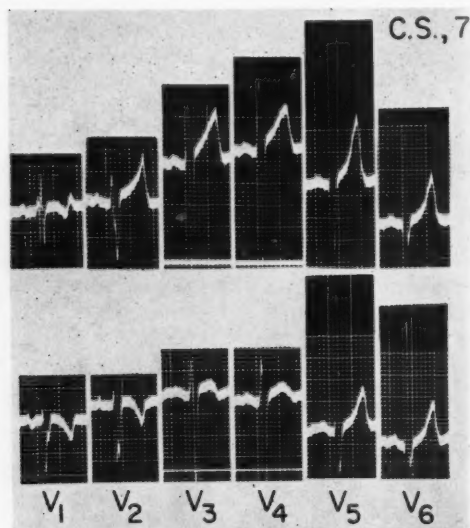
This paper presents a comparative study of the electrocardiograms of 90 patients before and after the surgical repair of their ventricular septal defects. Their ages ranged from 2 to 36 years with an average of 9. Sixteen-lead electrocardiograms were taken in most instances. A bubble oxygenator of the DeWall



**Figure 1A**

Lead  $V_1$  shows regression of the changes of "incomplete right bundle-branch block." (Top, before operation; middle, 2 weeks after operation; bottom, 2 months after operation.)

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**Figure 1B**

The secondary R wave in  $V_1$  disappeared after operation. (Top, before operation; bottom, 2 months after operation.)

Table 1  
Morphology of QRS Complex in  $V_1$

	Number of cases					Total
	rS	rSr'	rSR'‡	RS	R	
Isolated ventricular septal defect						
Before	11	1	10	28	2	52
After	22	5	19	4	2	
Ventricular septal defect with infundibular stenosis or valvular pulmonic stenosis						
Before	2	0	5	6	7	20
After	2	1	15	1	1	
Ventricular septal defect with pulmonary hypertension* with or without associated cardiovascular anomalies†						
Before	2	0	3	8	0	13
After	2	1	9	1	0	0
Ventricular septal defect with associated cardiovascular anomalies without pulmonary hypertension						
Before	0	0	1	4	0	5
After	1	0	4	0	0	

\*Pulmonary artery pressures in excess of 40 mm. Hg systolic.

<sup>†</sup>Associated cardiovascular anomalies included atrial septal defect, coarctation of the aorta, patent ductus arteriosus.

<sup>‡</sup>rSR' includes incomplete and complete right bundle-branch block and right ventricular hypertrophy.

type was used in each operation with flow rates calculated at approximately 50 ml. per Kg. of body weight. The perfusion time ranged from 10.5 to 55 minutes and averaged 23 minutes. No left ventricular cardiomyotomies were done. Cardiac arrest was induced in 26 patients, including 4 who had infundibular stenosis as well as ventricular septal defects. These patients have been followed from 6 weeks to 29 months after operation. The electrocardiograms were taken at return visits 1 to 3 months after operation and at later re-examinations if significant electrocardiographic changes were found earlier.

Table 1 lists the general configurations of the QRS complexes in lead  $V_1$  before operation and at the last examination. An rS complex is defined here as an initial positive deflection of less than 0.5 mv. in amplitude and smaller

than the associated S wave. Some of the electrocardiograms with large RS complexes in  $V_1$  were interpreted as right ventricular hypertrophy depending upon the age of the patient and the R/S ratio. Monophasic R waves typical of right ventricular hypertrophy were uncommon except in patients with a severe tetralogy of Fallot. The tracings with rSR' complexes were not interpreted as showing right bundle-branch block. Instead, we believe the r' deflection results from the electrical position or from degrees of hypertrophy in the region of the right ventricular outflow tract (the so-called crista pattern).<sup>1</sup> Tracings with rSR' complexes in  $V_1$  were interpreted as either right bundle-branch block or right ventricular hypertrophy depending upon the duration of the initial r wave and the amplitude and duration of the secondary R wave,

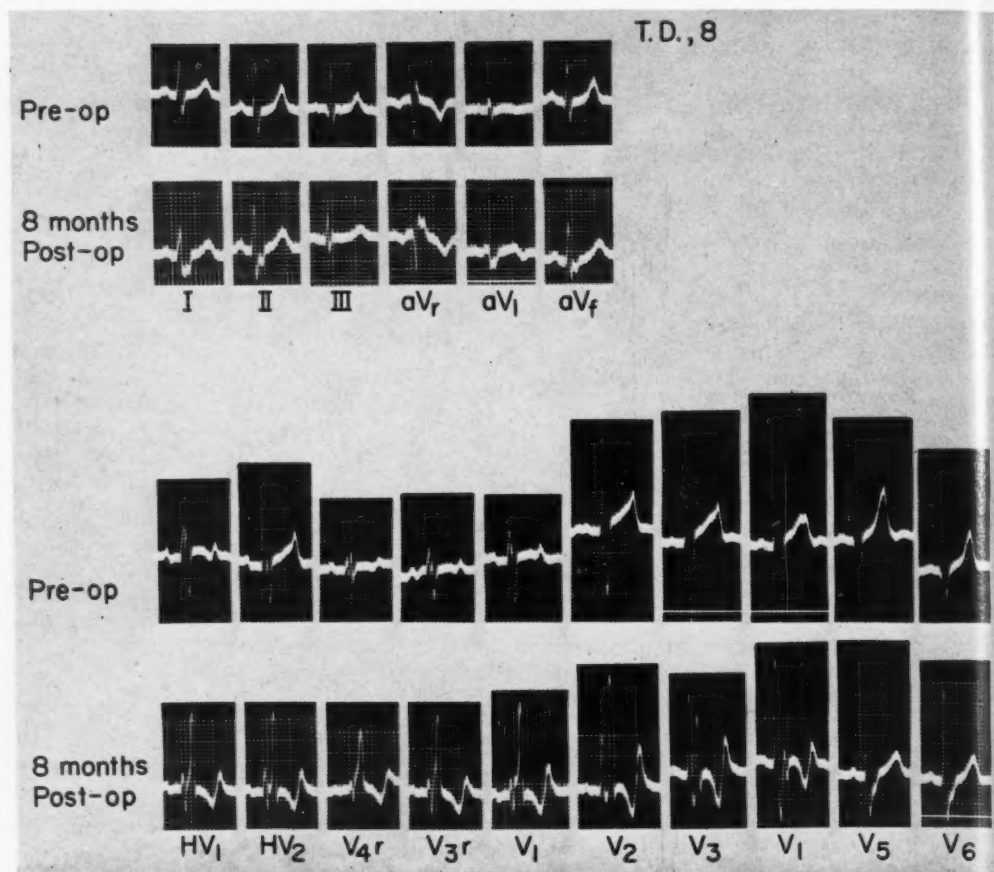


Figure 2

Complete right bundle-branch block with a QRS duration of 0.16 second appeared after operation.

according to the criteria of Myers.<sup>2</sup> An rSR' configuration in right ventricular leads without abnormal prolongation of the initial r wave but with increased amplitude and duration of the secondary R wave has been interpreted as evidence of right ventricular hypertrophy rather than bundle-branch block.<sup>3,4</sup> Diminution of the amplitude and duration of R' after surgery occurred in 7 of the patients in this study and is consistent with such a view point (fig. 1). These regressions toward normal have been overshadowed by the more frequent appearance of obvious conduction disturbances in right ventricular leads that

can be interpreted only as bundle-branch block (table 2). Some of these have been bizarre (fig. 2). Thirty-eight patients developed obvious bundle-branch block after surgery. Complete right bundle-branch block occurred most frequently in the group with ventricular septal defects associated with infundibular stenosis. These changes have persisted relatively unchanged.

T-wave abnormalities in precordial leads have been a common finding after operation in our series. The magnitude of the change frequently has exceeded what one might expect from thoracotomy and opening of the pericardium.

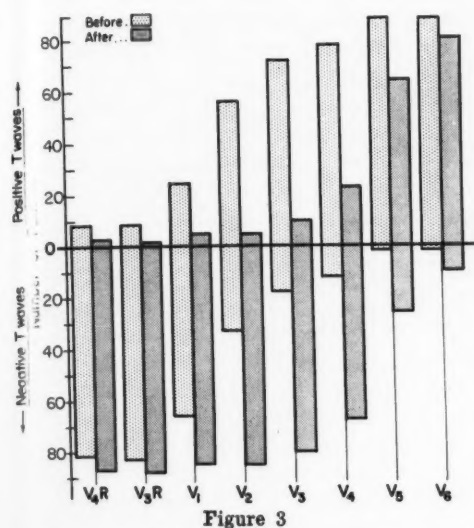


Figure 3

Tabulation of the polarity of T waves in precordial leads to show the changes that occurred after surgery. A small number of diphase T waves are included in the negative T-wave group.

dium alone. T-wave inversion through V<sub>4</sub> often is a normal finding in children and, indeed, when a positive T wave occurs in V<sub>1</sub> in an infant or small child, right ventricular hypertrophy may be present. Most of the patients had positive T waves in the transition zone and in leads to the left before surgery, but a very large number changed in this respect afterward, particularly in the transition zone (fig. 3). T-wave changes extending as far as V<sub>5</sub> and V<sub>6</sub> were common, being inverted in approximately 20 per cent. When positive T waves persisted in these leads, they were usually decreased in amplitude (fig. 4). In figure 5a and 5b, the depth and extent of T-wave inversion can hardly be considered normal.

"Pericarditis" is an unlikely explanation for the T-wave abnormalities, particularly since a large number of patients in our experience who have had atriotomy for the repair of atrial septal defects under hypothermia have not shown persistent T-wave changes. What then are the possible mechanisms for injury to muscle? Injury to conduction pathways in the muscular portion of the ventricular septum

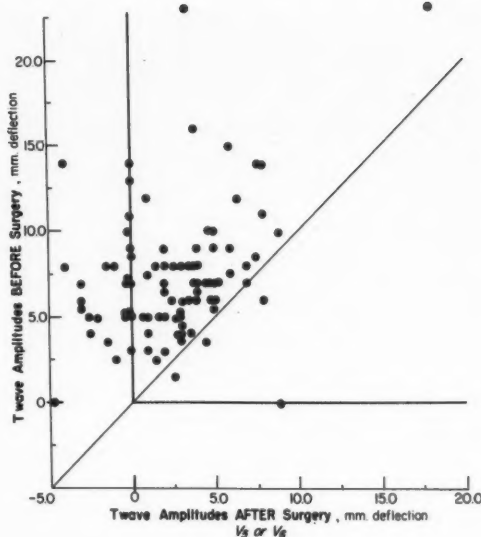


Figure 4

T-wave amplitude in left precordial leads decreased consistently after ventriculotomy.

from sutures placed in the rim of the defect can easily explain the bundle-branch block. Trauma to the myocardium from manipulation alone is probably minimal in most of our patients. Cardiac massage and electrical defibrillation are known to produce muscle damage, but these measures are seldom necessary when the pump oxygenator is used. Even in the mechanically inactive state, the heart continues to consume oxygen as long as it is available. Cardiac arrest with prolonged interruption of the blood supply to the heart muscle might therefore produce some degenerative changes even though the muscle is not contracting, but induced cardiac arrest was not a common denominator in the patients who showed some of the most extensive T-wave changes in the precordial leads. Coronary air embolism would seem to be another possible explanation for these changes. It has been observed on several occasions, and usually does not produce permanent damage, but it was associated with the electrocardiographic signs of myocardial infarction in 1 boy (fig. 6). Small bubbles in the coronary arteries may be "washed out" of the vascular bed if the per-

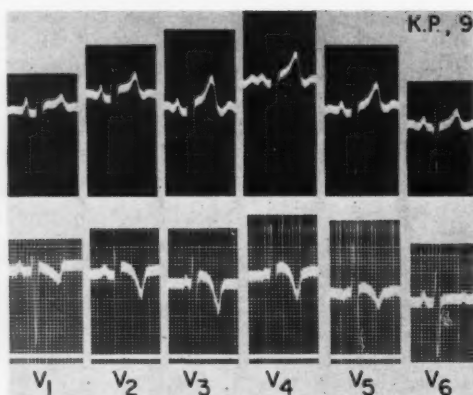


Figure 5A

Significant T-wave changes after ventriculotomy. (Top, before operation; bottom, 9 months after operation.)

fusion pressure is high enough, but removal by forcing the air on through to the venous side or by diffusion and solution of the gases may not be complete before the injury occurs.

A fatal myocardial infarction occurred in 1 girl due to extension of a thrombus into the left coronary artery (fig. 7). This thrombus originated in an area of aneurysmal dilatation of the aorta at the site of aortotomy for correction of an unsupported aortic cusp. Rarely aortic insufficiency appearing or increasing after operation on the basis of an unsupported aortic cusp accounts for some T-wave abnormalities (fig. 8). Myocardial damage from the incision in the free wall of the right ventricle might be associated with abnormalities in direct leads from this area, but would not be expected to produce widespread changes unless the blood supply to the adjacent areas is interrupted. Small branches of the right coronary artery are sometimes transected when ventriculotomy is done. Right ventriculotomy appears to be crucial to the electrocardiographic changes because they are less common in a smaller group of patients whose surgery included the extracorporeal pump but no ven-

Table 2  
Conduction Disturbances before and after Ventriculotomy

	Number of patients	Incomplete right bundle-branch block		Complete right bundle-branch block	
		No.	Per cent	No.	Per cent
Isolated ventricular septal defect	52				
Before		10	19	1	2
After		9	17	7	14
Ventricular septal defect with infundibular stenosis or valvular pulmonic stenosis	20				
Before		2	10	1	5
After		6	30	13	65
Ventricular septal defect with pulmonary hypertension with or without associated cardiovascular anomalies*	13				
Before		3	23	0	0
After		4	31	5	39
Ventricular septal defect with associated cardiovascular anomalies* without pulmonary hypertension	5				
Before		1	20	0	0
After		1	20	3	60

\*Associated cardiovascular anomalies included atrial septal defect, coarctation of the aorta, patent ductus arteriosus.

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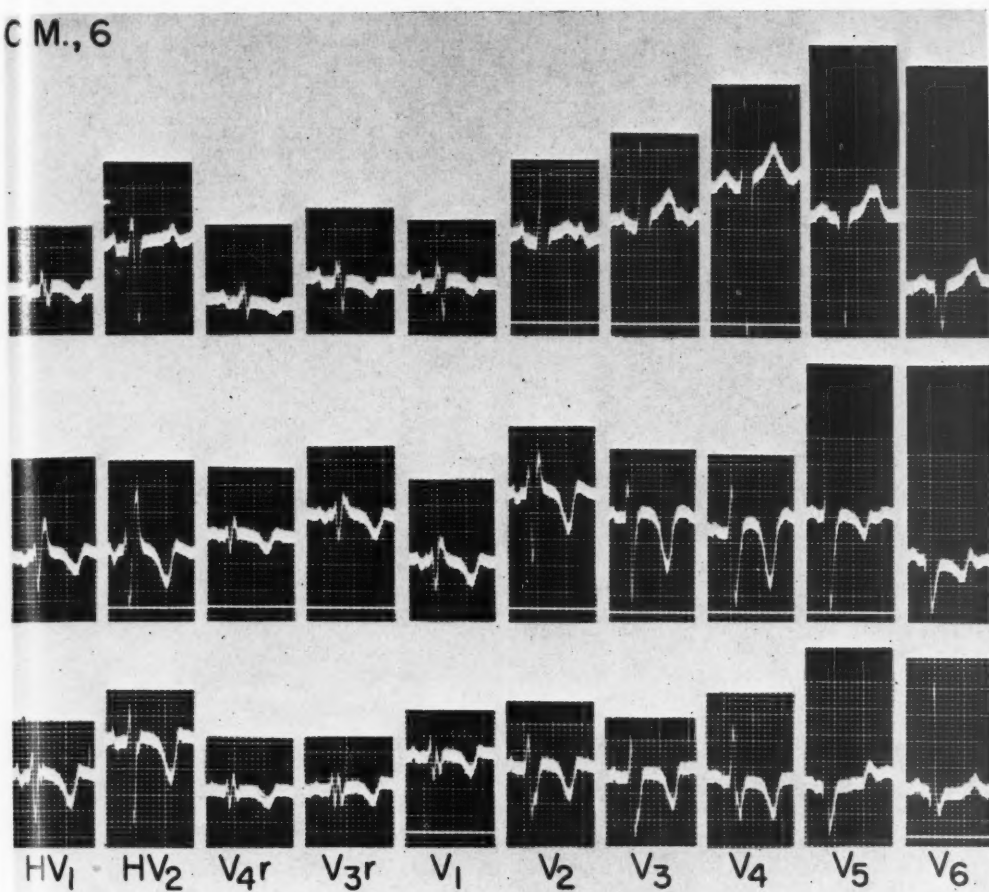


Figure 5B

*Significant T-wave changes after ventriculotomy. (Top, before operation; middle, 2 months after operation; bottom, 4 months after operation.)*

triculotomy. None of the above hypotheses logically accounts for all of the electrocardiographic abnormalities that have been encountered, and one is left with the impression that diffuse muscle damage may occur from ventriculotomy during cardiac bypass.

#### Summary

Right bundle-branch block appeared frequently after closure of ventricular septal defects, particularly in those patients who also had infundibular stenosis and in whom some of the infundibular muscle was resected. The magnitude of the postoperative changes of

right bundle-branch block indicates that a conduction disturbance was produced, probably as a result of interruption of pathways in the septum. These alterations are in contrast to the postoperative disappearance or regression of secondary R waves in rSR' complexes in other patients whose preoperative interpretation included incomplete right bundle-branch block. Regression of these abnormalities supports the view that right ventricular hypertrophy rather than delayed conduction through the septum was at fault in the beginning.

Extensive T-wave changes in precordial

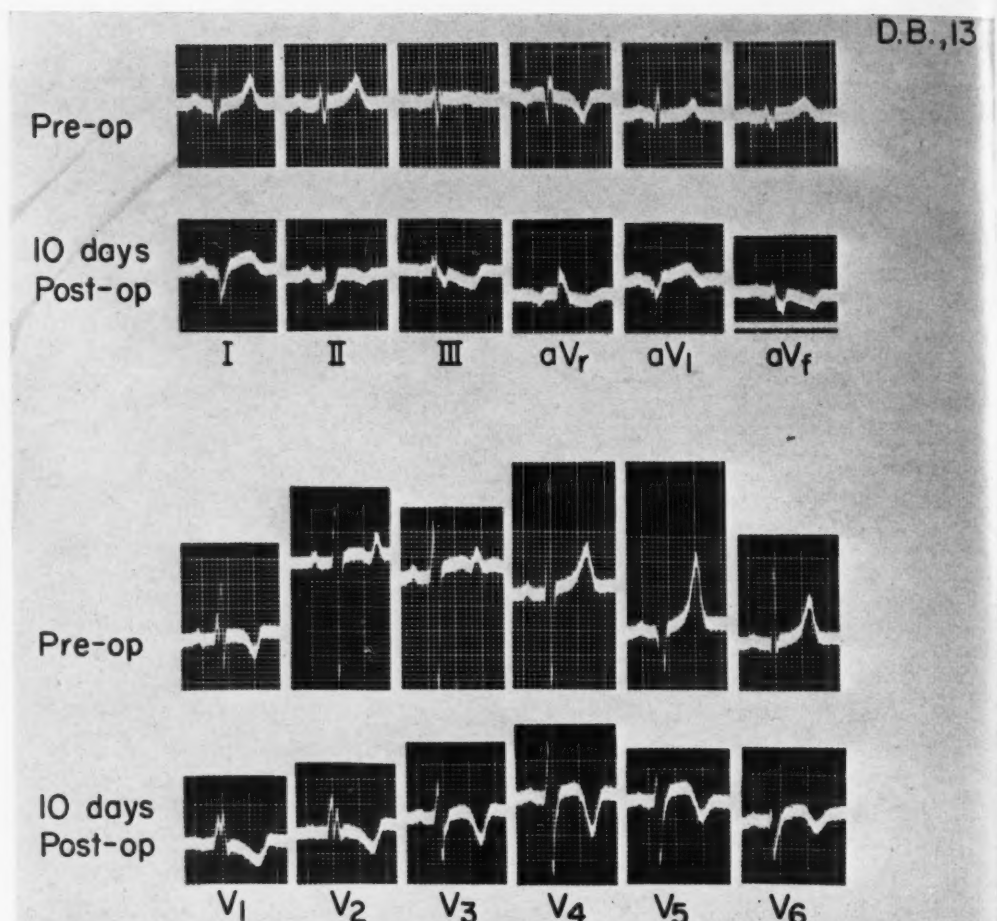


Figure 6

*Coronary air embolism was observed at operation. A short period of ventricular fibrillation followed. Electrocardiographic signs of myocardial infarction developed. Q waves appeared in leads I and  $aV_L$ . There were significant decreases in R-wave amplitude in left precordial leads.*

leads after right ventriculotomy and closure of ventricular septal defects indicate a significant alteration in ventricular repolarization. The extent and duration of these abnormalities cannot be explained by pericarditis, myocardial infarction, or the occasional development of left ventricular hypertrophy secondary to aortic insufficiency from an unsupported aortic cusp. T-wave abnormalities were more common than in a smaller group of patients in whom bubble oxygenators were used for

other operations, which did not include right ventriculotomy. Possible mechanisms for the production of the T-wave changes include injury to septal muscle from sutures, coronary air embolism, and muscle damage from the ventriculotomy itself.<sup>5</sup> Induced cardiac arrest, whether anoxic or drug-induced, does not have a direct relationship to these changes. The clinical course of these patients thus far indicates that these electrocardiographic changes have no prognostic significance.

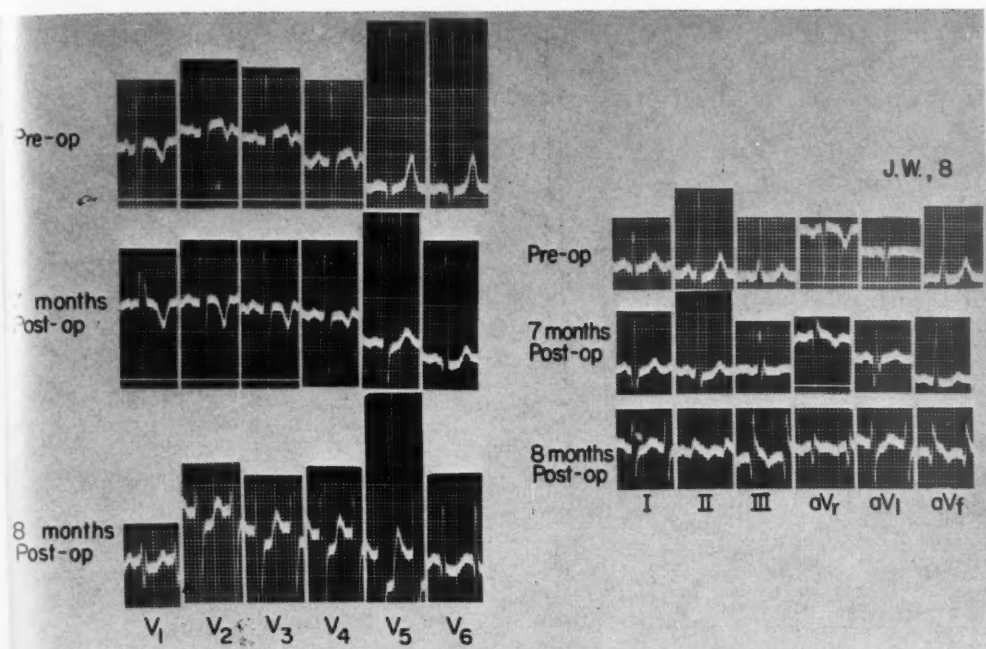


Figure 7

*Acute posterior myocardial infarction appeared 8 months after operation in this 8-year-old girl. An attempt had been made to relieve aortic insufficiency due to prolapse of the cusp adjacent to the defect by creating a bicuspid valve. Aneurysmal dilatation of the aorta developed at the site of the aortotomy. A thrombus formed and propagated into the left coronary artery causing death.*

### Summario in Interlingua

Bloco de branca dextere se manifestava frequentemente in le electrocardiogramma de patientes in qui clausura chirurgic de un defecto ventriculo-septal habeva essite effectuate, specialmente in casos in que stenosis infundibular esseva co-existente e in que un parte del musculo infundibular habeva essite resectionate. Le magnitudine del alterationes post-operatori in le electrocardiogrammas indica que le conduction esseva disturbate, probabilemente in consequentia de un interruption de circuitos in le septo. Iste alterationes contrasta con le disparition o regression post-operatori de secundari undas R in complexos de rSR' in altere patientes in qui le electrocardiogramma pre-operatori exhibiva manifestationes de incomplete bloco de branca dextere. Le regression de iste anormalitates supporta le conception que hypertrophia dextero-ventricular plus tosto que retardo del conduction in le septo esseva le vicio original.

Extense alterationes del unda T in derivationes recordial post ventriculotomia dextere e clausura de

defectos ventriculo-septal indica un alteration significative del repolarisation ventricular. Le grado e le duration de iste anormalitates non pote esser explicate per pericarditis, infarmento myocardial o le disveloppamento occasional de hypertrophia sinistro-ventricular secundari a insufficientia aortic in consequentia de un non-supportate cuspid aortic. Anormalitates del undas T esseva plus commun que in un altere e minus numerose gruppo de patientes in qui oxygenatores perlante habeva essite usate in operationes non requirente ventriculotomia dextere. Le possibile mecanismos responsabile pro le production del alterationes de unda T include lesiones del musculo septal per suturas, embolismo aeree coronari, e traumatismo muscular causate per le ventriculotomia mesme. Le induction de arresto cardiac (per anoxia o per drogas) non es directemente relationate con iste alterationes. Le curso clinic de iste patientes indica, usque nunc, que le mentionate alterationes electrocardiographic es disprove de signification prognostic.

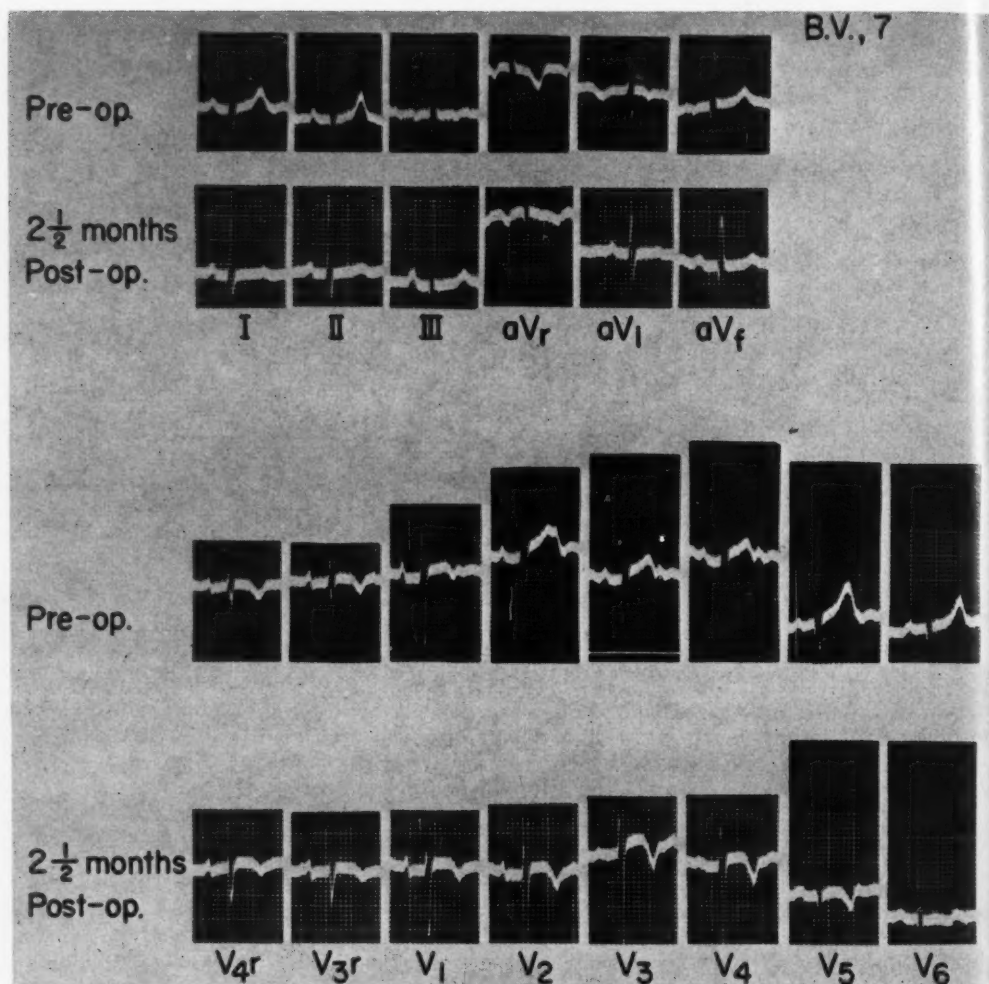


Figure 8

*This patient had aortic insufficiency because of a prolapsed cusp. The insufficiency increased after repair of the ventricular defect. This may account for the T-wave changes in left precordial leads.*

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# Blood Pressure in Bushmen of the Kalahari Desert

By BENJAMIN KAMINER, M.B., B.CH. (RAND.), AND  
W. P. W. LUTZ, M.Sc. (RAND.)

**T**HE FACTORS affecting and regulating arterial blood pressure are numerous and complex. Although much useful information has been accumulated about the relationship of blood pressure values to age, sex, weight, diet, occupation, emotional states, and heredity, no precise conclusions can be drawn at present about how these various factors produce high blood pressure.

In recent years it has become increasingly evident that useful information can be obtained about factors affecting blood pressure from a study of different ethnic groups particularly on the African continent. Several reports of the blood pressure in such ethnic groups have already been published.<sup>1-6</sup> The present report aims further at recording the blood pressure of groups of Bushmen living a nomadic life in the Kalahari Desert under conditions that are markedly different from those of the African, living in the urban and rural areas of Southern Africa.

## Material and Methods

The University of Witwatersrand 1958 Summer Expedition located 2 groups of Bushmen living under primitive conditions about 100 miles south of Ghanzi in the Kalahari, Bechuanaland Protectorate.

The Bushmen are a nomadic peaceful people who live in small self-contained groups of about 30 to 80 individuals including children. They are monogamous, with each family consisting of 1 to 3 children.

The Bushmen practice no form of agriculture. In the areas of the Kalahari where they live, the ground has not been cultivated in any way. Understandably, these people suffer from periods of plenty and scarcity, and the water supply and density of game determine their area of abode and migration. Consequently they lead a frugal exist-

ence, subsisting on game that is hunted and trapped, and on melons, roots, and other forms of wild vegetation. Each family builds an open type of shelter from tree branches, twigs, and straw, which acts as a windbreak, and after migration the shelters are abandoned. The Bushmen are exposed to extreme heat during the day and to intense cold at night. Examples of the diurnal variation in temperature are 5 to 35 C. in the summer and 3 to 23 C. in the winter. The Bushmen adjust to the cold by the use of skin cloaks and wood fires.<sup>7</sup>

Through periodic contact with Europeans and other Africans, the men and women and even children have acquired the habit of smoking when tobacco is available. The Bushmen do not drink any form of alcoholic brew. These few observations on the way of life of the Bushmen are cited as background that may possibly have some relevance to the present study. Further details relating to the habits of Bushmen may be obtained elsewhere.<sup>8-11</sup>

In the 2 nomadic Bushmen groups, 42 males and 36 females were investigated. While the numbers are comparatively small, each nomadic group was a completely self-contained socioeconomic unit. From this point of view, therefore, a complete population was investigated. Hence there was no problem of sampling, which usually arises in most contemporary studies, where such factors as differences in occupation in the city and rural areas and also variations in income, diet, and mode of living must be sorted out and correlated. The homogeneity of the Bushmen groups, from the point of view of occupation and mode of living, does not, however, compensate for the inherent deficiencies in the statistical analysis of small numbers, as will be indicated, and hence the need exists for more extensive investigations. A third group of Bushmen consisting of 21 male farm laborers and prisoners in Ghanzi was also examined. Interrelationship by blood or marriage has been ignored and the data have been treated statistically as a random selection of individuals from a large population. Furthermore, it has been assumed that the data are normally distributed or at least approximately so.

As it was not possible to obtain information on the ages of the Bushmen, 3 independent observers made an assessment of their ages based on the

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Table 1

*Blood Pressure of Nomadic Bushmen*

Item	Systolic (mm. Hg)				Diastolic (mm. Hg)				Pulse pressure (mm. Hg)			
	Adolescents 12-17 yrs.	Young adults 18-35 yrs.	Middle-aged 40-55 yrs.	Old-aged 60+ yrs.	Adolescents 12-17 yrs.	Young adults 18-35 yrs.	Middle-aged 40-55 yrs.	Old-aged 60+ yrs.	Adolescents 12-17 yrs.	Young adults 18-35 yrs.	Middle-aged 40-55 yrs.	Old-aged 60+ yrs.
Males												
Sample size	4	14	13	11	4	14	13	11	4	14	13	11
Mean	107.5	110.1	107.5	107.6	68.0	66.9	63.1	67.8	39.5	43.3	44.5	39.8
Variance	223	137	125	98	179	28	45	30	49	45	76	54
S.D.	14.9	11.7	11.2	9.9	13.4	5.3	6.7	5.5	7.0	6.7	8.7	7.3
Females												
Sample size	7	12	8	9	7	12	8	9	7	12	8	9
Mean	108.3	112.0	117.5	113.8	69.7	68.8	70.8	69.6	38.6	43.2	46.3	44.2
Variance	82	226	166	370	79	71	32	81	74	131	152	165
S.D.	9.1	15.0	12.9	19.2	8.9	8.7	5.7	9.0	8.6	11.5	12.3	12.9

Table 2

*Blood Pressure of Bushmen Prisoners and Farm Laborers*

Item	Systolic (mm. Hg)		Diastolic (mm. Hg)	
	Young adults (18-37 yrs.)	Middle-aged (40-55 yrs.)	Young adults (18-35 yrs.)	Middle-aged (40-55 yrs.)
Males				
Sample size	14	7	14	7
Mean	123.4	119.1	71.7	68.6
Variance	91	58	58	30
S.D.	9.5	7.6	7.6	5.5

skin characteristics and hair color, and in addition a dentist examined the teeth, particularly their number, state of eruption, and degree of crown wear. By these means the Bushmen were broadly grouped into adolescents (12 to 17 years approximately); young adults (18 to 35 years approximately); middle-aged (40 to 55 years approximately); old-aged (approximately 60 years and over). It was subsequently assumed that the approximate midpoint of these age groups could be taken as 15, 25, 45, and 65 years, respectively.

The blood pressure of each subject was taken while he was reclining on a stretcher after a rest period of about 10 minutes. Single blood pressure readings were made by means of a mercury sphygmomanometer with a cuff size of 13 cm. by 24 cm.

The systolic pressure was taken when the first sound was detected on deflation of the cuff and the diastolic pressure was taken as that point at which muffling of sound occurred (stage IV). The atmospheric temperature during the examination varied on the average between 21 and 30 C. Height,

weight, and arm girth were determined by other members of the expedition.

**Results**

In table 1 are set out the systolic, diastolic, and pulse pressures according to sex and age. The group of 21 laborers and prisoners is treated separately (table 2). The average systolic pressures for the nomadic Bushmen were 108.4 mm. Hg (S.D. 11.4) for males and 112.8 (S.D. 14.6) for females. The mean diastolic pressures were 66.2 mm. Hg (S.D. 6.9) and 69.6 (S.D. 8.0) for males and females respectively. Examples of the highest pressures obtained are 140 systolic, 78 diastolic in the case of an old woman and 134 systolic, 80 diastolic in the case of a young adult.

**Effect of Age on Blood Pressure***Systolic Pressure*

From table 1 it is obvious that the systolic blood pressure of the men showed no tendency to rise with age. Statistical analysis of the systolic blood pressure in women likewise showed no rise in pressure with age. Student's test on the largest and smallest observed means of the women, that is 117.0 and 108.3 respectively, gave  $t=1.4$ , which is certainly not significant. As a further test, a straight line (least squares) was fitted to the systolic pressures and age in women (mid-points being the ages 15, 25, 45, and 65). An estimated slope of 0.0105 was obtained having an estimated variance of .0172. Hence the contention

Table 3

Comparison of Blood Pressures in Males and Females

Item	Systolic (mm. Hg)	Diastolic (mm. Hg)
all		
Sample size	42	42
Mean	108.4	66.0
Variance	172.0	55.8
S.D.	13.1	7.5
males		
Sample size	36	36
Mean	112.8	69.6
Variance	172.0	55.8
S.D.	13.1	7.5
t-value	1.48	2.12

that the systolic pressure of women does not increase with age is not rejected by the observations on this comparatively small group. The mean of the systolic pressures for women, however, did show a *slight* increase toward middle age, with a subsequent decrease in old age (table 1).

#### Diastolic Pressure

Table 1 again illustrates no tendency for the diastolic pressures to rise with age; the means were very stable.

#### Pulse Pressure

The pulse pressure likewise does not increase with age (table 1).

#### Comparison of Men and Women

Based on statistical tests the assumption could reasonably be made that variances in men and women were estimates of the same population variance. It is suspected, however, that the data for women are more variable than for men and that agreement is obtained in this case because of the small size of the sample. Nevertheless, it was decided to combine the variances of the sexes to give a pooled estimate of 172 mm. Hg for the systolic and 55.8 mm. Hg for the diastolic pressures (table 1). Examination of table 1 shows that in general the means for women exceed the corresponding means for men for the systolic and diastolic pressures. Since no trend with age was found, the means of all ages were combined and set out in table 3.

Table 4

Weight/Height (W/H) of Nomadic Bushmen

Item	Young adult (18-35 yrs.)	Middle-aged (40-55 yrs.)	Old-aged (60 yrs. +)	Average
Males				
Sample size	14	13	10	37
Mean	297	303	296	298.6
Variance	—	—	—	768
S.D.	—	—	—	27.7
Females				
Sample size	9	8	9	26
Mean	276	275	286	297.1
Variance	—	—	—	688
S.D.	—	—	—	26.21
t-value	—	—	—	2.8

Table 5

Arm Girth and Weight (W/H) Relationships

Item	Correlation	Regression slope of arm-girth on W/H	Variance of slope
Males	0.75	0.454	0.00501
Females	0.71	0.345	0.00505
		t=0.35	

The diastolic t-value is significant at the 95 per cent level and suggests that diastolic pressures in women exceed the mean pressure in men by 3 to 4 units. While the systolic t-value is not significant, it is likely that if a larger group were examined, the mean systolic pressure in women would also exceed mean pressure in men by about 3 to 4 units. Some further evidence to support this supposition is based on examining the "corrected" pressure later on and also on the agreement between men and women of uncorrected pulse pressure.

#### Relationship of Blood Pressure to Height and Weight in the Adults

The average height of adult male Bushmen was 157.9 cm. (S.D. 2.6) and adult women 147.9 cm. (S.D. 6.7). The average weights for men and women were 47.1 Kg. (S.D. 4.8) and 41.3 Kg. (S.D. 5.0), respectively. After adolescence, therefore, weight does not apparently increase with age.

In table 4 are illustrated the weight/height

**Table 6**  
*Blood Pressures "Corrected" for Arm Girth Nomadic Bushmen, excluding Adolescents*

Item	Systolic (mm. Hg)			Diastolic (mm. Hg)			Pulse pressure (mm. Hg)		
	Young adults (18-35 yrs.)	Middle-aged (40-55 yrs.)	Old-aged (60 + yrs.)	Young adults (18-35 yrs.)	Middle-aged (40-55 yrs.)	Old-aged (60 + yrs.)	Young adults (18-35 yrs.)	Middle-aged (40-55 yrs.)	Old-aged (60 + yrs.)
<b>Males</b>									
Sample size	14	13	11	14	13	11	14	13	11
Mean	116.2	112.5	113.1	61.5	58.5	63.3	54.7	54.1	49.8
Variance	157	87	72	40	39	22	54	66	54
S.D.	12.5	9.3	8.5	6.3	6.2	4.7	7.3	8.1	7.3
<b>Females</b>									
Sample size	10	7	9	10	7	9	10	7	9
Mean	121.6	129.3	123.6	67.9	70.0	66.8	53.7	59.3	56.8
Variance	250	92	350	76	45	105	102	138	149
S.D.	15.8	9.6	18.7	8.7	6.7	10.3	10.1	11.75	12.2

ratio (W/H) for adults only. The difference between averages for adult men and women was found to be significant. Thus women with blood pressure greater than that in men were in fact lighter in weight.

Scatter diagrams were drawn of the uncorrected systolic and diastolic pressures for men and women against the W/H ratio. Although a slight positive trend was observed with increasing W/H, in no case was the slope found to be significantly different from zero.

#### Examination of the Data "Corrected" for Arm Girth

"Corrections" for arm girth were made according to Pickering<sup>12</sup> based on the data from Ragan and Bordley.<sup>13</sup> It still needs to be determined whether these corrections for arm girth apply to the population of Bushmen. Scattergrams of systolic and diastolic pressures against arm girth of our series of Bushmen did not reveal any relationship between blood pressure and arm girth. Scattergrams of arm girth against W/H were also examined and the results are depicted in table 5. As expected, the slopes are significantly different from zero, as are also the correlation coefficients. The figures for men and women agree very well with respect to the correlation and the difference in the slopes between the men and women is not significant. Due to the relatively small arm girths, the corrected systolic is slightly higher and the corrected diastolic

lower than the corresponding series of uncorrected pressures (tables 6 and 1).

#### Effect of Age

Again age does not influence the mean value of the readings of any of the "corrected" pressures (table 6).

#### Sex Comparison

For sex comparison of the "corrected" blood pressures, all 3 age groups were combined, since age did not appear to affect the readings (table 7).

The observed variances for men and women approach the 95 per cent significant difference level in the case of the systolic pressure and hence the ordinary normal theory u-test was used, which does not assume equality of variance. Also the number of cases available for analysis decreased, since arm girths were not measured in every case.

These data suggest that while the mean "corrected" systolic and diastolic pressures for women are above the corresponding figures for men, the pulse pressures show no statistically significant sex difference. Whether there is, in fact, a sex difference in the pressure, can only be decided when a larger series of Bushmen are examined.

#### Comparison of Male Prisoners and Farm Laborers with Nomadic Male Bushmen

Student's test shows that there was no difference between the young adult and middle-

Table 7

*Comparison of Blood Pressures in Males and Females "Corrected" for Arm Girth*

Item	Systolic (mm. Hg)	Diastolic (mm. Hg)	Pulse pressure (mm. Hg)
<b>Males</b>			
Sample size	38	38	38
Mean	114.1	61.0	53.1
Variance	104.0	48.2	56.0
S.D.	10.2	6.9	7.5
<b>Females</b>			
Sample size	26	26	26
Mean	124.3	68.1	56.3
Variance	246.9	78.9	81.3
S.D.	15.7	8.9	9.0
u - value	2.92	3.4	1.49

aged prisoners and laborers (table 2). Hence for further comparison the 2 age groups were combined. Since age did not appear to influence the nomadic Bushmen pressures, the 4 age groups were combined to give a total of 42 nomadic male Bushmen. The pooled estimates obtained are given in table 8.

The observed t-values are certainly significant; there appears to be a marked difference (at least at the time the readings were taken) between the prisoners and laborers on the one hand and the nomadic Bushmen on the other with respect to both diastolic and systolic pressures. There was no significant difference in arm girth and W/H ratio between this group and the nomadic groups to account for the observed differences in pressure.

#### Discussion

Results obtained from population studies of blood pressure are not always strictly comparable because of differences in sampling techniques and in the methods of recording and reporting the blood pressure. Nevertheless, reviewers of the literature<sup>12, 14-16</sup> have been able to point out that the blood pressure readings in some populations, like the Chinese,<sup>17</sup> seem to be lower than those found in people living in Western countries and that Negroes have higher pressures than the white populations in America.<sup>18, 19</sup> It is also recognized that Negroes suffer commonly from essential hypertension as do also the Africans (Bantu) living in South Africa.<sup>5, 6</sup>

Table 8

*Comparison of Male Prisoners and Farm Laborers with Nomadic Male Bushmen*

Item	Systolic (mm. Hg)	Diastolic (mm. Hg)
<b>Prisoners and laborers</b>		
Sample size	21	21
Mean	122.0	70.7
Variance	80.6	48.7
S.D.	9.0	7.0
<b>Nomadic</b>		
Sample size	42	42
Mean	108.4	66.0
Variance	130	46.0
S.D.	11.4	6.8
t - value	4.78	2.57

The low mean values of the systolic and diastolic pressures in the nomadic Bushmen groups are comparable to those reported for the Chinese populations mentioned above. The mean pressures of the Bushmen including the values "corrected" for arm girth are lower than those reported for other Africans in South Africa,<sup>6</sup> Kenya,<sup>1</sup> Uganda,<sup>3</sup> and for Aborigines in Australia,<sup>20</sup> and Eskimos in Labrador, Greenland, and Alaska.<sup>21, 22</sup> The cause of the low blood pressure remains to be determined, but a possible contributing factor is the smallness in stature and lightness of weight, which is also a feature of the Chinese.<sup>23</sup> The higher pressures in the women despite their lighter weight, as compared to the men, might be related to their lesser degree of physical activity.<sup>24</sup>

The blood pressure in the Bushmen does not appear to increase with age, a feature in marked contrast to that described in European<sup>25, 26</sup> and in American populations,<sup>27</sup> where blood pressure is a "graded characteristic" continuously increasing with age.

In view of the observations in the Bushmen and those of others in some African,<sup>1, 3</sup> Chinese,<sup>17</sup> and Ceylonese people,<sup>28</sup> the generalization is not acceptable that a rise in blood pressure is an inevitable concomitant of aging in a population. There is no a priori reason why the normal blood pressure should rise with age. There is neither structural nor functional evidence on the aging process to

account for a rise in arterial pressure in terms of factors that would increase the cardiac output or the peripheral resistance. Admittedly, some rise in the systolic pressure can be explained on the basis of loss of elasticity of the large arteries with age but the loss of elasticity may be offset in part by an accompanying enlargement of the cross-sectional area of the vessels.<sup>20</sup>

The conclusions of Robinson and Bruce<sup>30</sup> that normal blood pressure does not rise with age was criticized on the basis that their study was on a selected section of a population. This criticism of bias in sampling methods, however, does not apply in this present study. Hence the suggestion is again made that a rise in blood pressure with age may not be characteristic of a normal aging process but may itself be a manifestation of essential hypertension within a population.

Even though the groups studied were small, there can be no doubt that the Bushmen prisoners and farm laborers registered higher pressures than the nomadic Bushmen. The explanation for this finding may lie in the possibility that the conditions of recording the blood pressure were not strictly comparable for both groups. The nomadic Bushmen had become acquainted with our investigatory group over a period of several days before the blood pressure was measured, a condition that did not apply to the prisoners and laborers. Alternatively, the significant differences in the blood pressures of these 2 groups may be a consequence of the altered life of the laborers and the prisoners as compared with the nomads.

A further study of the physiology of the Bushmen may not only shed light on the influence of age on blood pressure but also on the relationship of environmental and genetic factors to those pathologic processes like heart or other diseases that are taking such a heavy toll of life in the Western world.

#### Summary

The blood pressure was studied in 42 males and 36 females in 2 groups of nomadic Bushmen, living near Ghanzi in the Kalahari Des-

ert, as well as in a third group of 21 Bushmen prisoners and farm laborers from the same region. The pressures were also "corrected" for arm girth.

The average systolic pressures were 108.4 mm. Hg (S.D. 11.4) for men and 112.8 mm. Hg (S.D. 14.6) for women. The average diastolic pressures were 66.2 mm. Hg (S.D. 6.9) and 69.6 mm. Hg (S.D. 8.0) for men and women, respectively. These pressures with stated exception, are considered to be lower than for most populations.

In the women, the systolic and diastolic pressures were higher than those in the men.

The blood pressure showed no tendency to rise with age, an observation in contrast to that found in most other populations. It was suggested that an increase of the blood pressure with age may be an indication of the existence of essential hypertension within that population.

The blood pressures of Bushmen prisoners and farm laborers were higher than those in nomadic Bushmen.

Further investigation is needed of the genetic and environmental factors affecting the blood pressure in the nomadic Bushmen.

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#### Summary in Interlingua

Le tension del sanguine esseva studiate in 42 masculos e 36 femininas in 2 grupos de boschimanos nomadic vivente in le vicinitate de Ghanzi in le deserto Kalahari e etiam in un tertie gruppo de 21 boschimanos prisioneros e obreros de ferma ab le mesme region. Le mesurationes esseva etiam corrigite pro differentias del circumferentia bracial.

Le tensiones systolic medie esseva 108,4 mm de Hg (D.S. 11,4) pro homines e 112,8 mm de Hg (D.S. 14,6) pro feminas. Le tensiones diastolic medie esseva 66,2 mm de Hg (D.S. 6,9) pro homines e 69,6 mm

d. Hg (D.S. 8,0) pro feminas. Iste valores (con exceptiones listate) pare esser plus basse que illos de alie populationes.

In le feminas tanto le tension systolic como etiam le tension diastolic esseva plus alte que in le homines.

Le tension del sanguine monstrava nulle tendentia de montar con le etate. Iste constatation es le contrario de lo que es trovate in le majoritate del altere populationes. Es suggerite que un augmento del tension del sanguine con le avantiamento del etate es possiblementemente un indication pro le existentia de hypertension essential intra le population in question.

Le tension del sanguine in boschimanos prisioneros e obreros de ferma esseva plus alte que illos in boschimanos nomadic.

Investigationes additional es requirite pro clarificar le factores genetic e ambiental que affice le tension del sanguine in le boschimanos nomadic.

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## SYMPOSIUM ON CORONARY HEART DISEASE

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### The Importance of Heredity in Coronary Heart Disease

By PAUL D. WHITE, M.D.

THE VITAL but neglected subject of the place of heredity in the background of coronary heart disease needs to be brought into the limelight to share at least on even terms in research with the sum of the possible environmental factors now being studied. Incidentally this is true of many other of the diseases of mankind in which the individual or host seems to have been lost in the preoccupation with the disease process. Practicing physicians not much given to intensive or extensive scientific research have had a long experience with so-called hereditary predisposition but either they must take up the subject more actively themselves or a new generation of human geneticists must be trained to help them; probably both these developments are needed.

One brief statement should be made in distinguishing between congenital and hereditary heart disease. The former may be hereditary or it may be the result of an acquired disease during fetal life.

There has recently been published a little book entitled *The Chemistry of Heredity* by Professor Stephen Zamenhof of Columbia University dedicated "to the enlightened programs of research grants in our country whose support made possible most of the recent discoveries in the field of the chemistry of heredity." Among the hereditary defects in man he cites alphabetically a list of 18 abnormalities beginning with albinism, which is due to failure to manufacture melanin, and ending with Wilson's disease, which is

due to defective copper metabolism. In the middle of this alphabetical list is hypercholesteremia, simply stated as elevated blood cholesterol, still quite obscure as an inherited chemical defect but clinically well recognized as often related to coronary heart disease. He writes further as follows:

In all the above considerations we have referred to the "failure of the enzyme" or "lack of enzyme." However, the lack of enzyme does not necessarily mean that the molecule of the enzyme, or of the protein in general) is missing altogether; it may often mean that it is defective, i.e. changed so as to be partially or totally inactive. Just how much has to be changed to cause inactivation? What is the smallest change in the protein which the mutation has to produce to make itself drastically felt?

One example of the answer to these questions has been provided by a study of a hereditary disease called sickle cell anemia. This disease, caused by a single mutant gene, is characterized by the presence of defective erythrocytes which are in the form of sickles. The defect was traced to defective hemoglobin and the problem was to determine what is the chemical nature of the difference between this defective and the normal hemoglobin.

Pauling and his colleagues subjected the two kinds of hemoglobin to electrophoresis and found that the two have different electric charges. This behavior suggested some difference in the amino-acid composition. But how many were different? And which ones? A molecule of hemoglobin has some 600 amino acids of 190 different kinds, and the problem might have appeared hopeless. It was solved eight years later by Ingram who broke the molecule in half, and then into 29 smaller fragments (peptides). When such fragments from normal hemoglobin were compared with the corresponding fragments from the defective hemoglobin, all were identical, *except one*. And in this fragment, all amino acids were identical, *except one*. Thus, the disease was caused by a change of one amino acid in 300 (glutamic acid replaced by valine). This was all the mutation had to do to

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make itself seriously felt. One is tempted to speculate that the corresponding change in the hereditary determinant (DNA molecule) was just as small; perhaps it was a change in a single nucleotide.

All this is a mere beginning. But the beginning has been made. And one is inclined to agree with Albert Einstein that the most incomprehensible thing about nature is that it is . . . comprehensible.

An apology to the reader. For the book being so long, yet failing to offer real answers to many formulated queries. The writer's excuse is that the subject is but an infant; if we have become able to ask nature embarrassing questions, it is already a crack in the wall. And an apology for the book being so short. The discussion of many hereditary diseases and of the cancer field has been omitted, partially because these subjects belong to special treatises, and partially because their connection with the chemistry of heredity is merely the object of future study.

A few months ago in Mexico City Dr. Irvine Page referred to this very point and suggested the eventual possibility of correcting the inherited defect and supplying the missing enzyme, which would mean a much more hopeful future for those who had not selected the most healthy ancestors. Just think what this may mean not only in our struggle against cardiovascular disease but in almost the entire range of the hazards to our health and to our very lives.

The practical aspects of heredity and coronary heart disease are, of course, a very different matter and they are beginning to be recognized. We practitioners know from experience the importance of heredity.

Thomas and Cohen found in their study that coronary heart disease was nearly four times more frequent among the siblings of individuals with coronary heart disease than among the siblings of persons not so affected. Thomas has studied in general the combined conditions of hypertension and coronary heart disease in a long-term follow-up of Johns Hopkins medical students with particular reference to the health of grandparents, parents, aunts, and uncles. She wrote,

In our analysis of the combined occurrence of hypertension and coronary heart disease in these two successive generations, the proportion of affected offspring was greatest where both parents

suffered from some form of these disorders, and least where neither parent was affected. According to whether both, one, or neither of the parents was affected, the incidence in the offspring was 22%, 12%, and 8% respectively. Thus, 2.7 times as many offspring of two positive parents were affected by hypertension or coronary disease as were the offspring of two negative parents. The rate for those with one positive parent was intermediate (1.5:1).

Also coronary heart disease was much more common among the fathers of the students with than among those without hypercholesteremia by more than twice in the case of the students over 22 years of age.

Russek in a recent paper comparing 100 patients with coronary heart disease with a comparable 100 patients with other diseases found heredity as a possible factor in a ratio of 1.7 to 1. In his study he attributed greater influence to stress 4.6 to 1 and high-fat diet 2.7 to 1.

In a paper of my own entitled *Genes, The Heart, and Destiny*, published two years ago in the *New England Journal of Medicine*, I wrote as follows:

A few years ago in a study of our own of coronary heart disease among 100 young adults (under the age of forty years) compared with 146 controls, it was found that 37 per cent of the fathers in the coronary group died from coronary heart disease as compared with 18.5 per cent in the control group (of 62 dead fathers of the coronary group, 23 had succumbed to coronary heart disease in contrast to only 14 out of 76 among the controls). Five out of 58 dead siblings of the coronary group died of coronary heart disease (8.6 per cent) in contrast to but 1 (1.0 per cent) among 98 siblings in the control group. We included only 1 case of recognized familial xanthomatosis or hypercholesterolemia in this series. Eighteen of the patients with coronary heart disease had serum cholesterol levels of more than 330 mg. per 10 ml. (one was as high as 509 mg.) as compared with five of the matched controls. It is, of course, well known that in familial hypercholesterolemia and xanthomatosis coronary heart disease is common.

In every study of coronary heart disease in youth and middle age the male sex is represented in high preponderance—for example, in our series referred to above, in the ratio of 24 to 1 under the age of forty years, though with much lowered ratio in the next two or three decades. The sex factor is much more significant than he-

redity, however. Two other characteristics often noted, which are inherited, are a highly mesomorphic (broad muscular) build and a psychologic and physiologic drive; these are probably but manifestations of the candidate rather than causative factors as may well be a tendency, that seems to be commonly found, to excesses in many habits that may be aggravating rather than basic factors, such as excesses in eating, smoking, and the use of alcoholic liquor.

It seems very probable that in the present almost frantic search, which, I might add, is highly important and should go on, to establish a safe program of life for the protection of our citizens from the present devastating epidemic of coronary thrombosis, we should not expect to find one program equally suited to all. It is a very complicated business, for we are dealing with the intricacies of diet, of stress and strain, of physical and mental effects, of climate, of infections, and of personal habits in addition to all manner of humankind, but the main point I want to make is that we must recognize our duty in the study of the host as well as in that of the agent (or environment), just as we would do in an infectious epidemic. Doubtless, there are general measures of positive health that are good for everyone and certain dangers that are bad and should be avoided, and these are at least in part already evident but the details of both host and agent are still to be added. We can supply, much more than we are doing now, the important ancestral and immediate family history in every case; this is bound to be helpful at the very start.

Although this is a truism recognized by every practicing physician it is astonishing how little attention is paid to it when we obtain and record the history of the individual patient. Often, though by no means always, we are in the habit of noting the age at and the cause of death, or the current state of health of parents and siblings, but rarely is this information noted for the grandparents or other relatives, despite its importance. To be sure, such information is at times unobtainable, but even when it is obtainable it is not often recorded.

Here, I would enter a plea to the public at large. In the first place a family genealogic record or tree would be very helpful for the doctor; it has much more than sentimental value, for it helps to determine the health hazards for descendants for generations to come. We physicians should spread the importance of this far and wide. A second valuable aid concerning the future health of any family is the information to be derived from postmortem examinations; the natural emotional reaction of the family at the time of death should not obscure the importance of these examinations after death. Even as far back as 1706,

over two hundred and fifty years ago, the Church, in the person of Pope Clement XI, urged the carrying out of autopsies to obtain invaluable information; this was done by his physician, Giovanni Maria Lancisi, and churchmen and scientists alike still strongly recommend to the public that such examinations be done.

For the sake of argument let us suppose that on the average, heredity and environment are equally responsible for both the maintenance of health, the induction of disease, and the length of life in mankind as a whole but with very variable influences in any given person.

However, this ratio of the relative importance of heredity and environment in the acquisition of coronary heart disease is a pure and simple guess. We should make every effort to determine the true ratio. Quite likely it varies very much in different individuals but in any case heredity is of great importance and its influence must not be neglected in the appraisal of any individual whether only a candidate or actually a patient.

Before concluding I would like to mention one other point or factor that may eventually prove to be of much greater significance than we may now realize and that has been almost not at all investigated. That is the actual anatomic configuration of the coronary arterial tree and network, which very probably is in part at least a familial inheritance. A study of this possibility is greatly needed. As an example of this let me cite the case of a patient of mine who died suddenly less than a fortnight ago during moderate physical exertion. He had suffered myocardial infarction of moderate degree a few years ago but had had a good recovery except for some residual cardiac hypertrophy and a slight limitation of myocardial reserve. Autopsy revealed acute pulmonary edema, no fresh coronary thrombosis, but a relatively small atheromatous left coronary artery tree and network; the right coronary artery was much larger than the left. May not this restricted left coronary arterial blood supply, congenital in origin, have played an important role? Let me quote in this connection from a recent publication of Professor Victor McKusick of Johns Hopkins University:

Genetically determined differences in the anat-

omy of the coronary arterial tree might account for its increased vulnerability to the effects of atherosclerosis. Direct evidence on familial similarities in coronary anatomy is not available and obviously is difficult to obtain. Demonstrations of the hereditary basis of other vascular patterns in man, such as that of the anterior chest wall, the antecubital fossa, the aortic arch, and the hand of the fetus, provide a precedent. In man, three patterns of major coronary branching have been identified: 1) right coronary artery predominant; 2) balanced coronary artery pattern; and 3) left coronary artery predominant. Hearts with the third type are most vulnerable to fatal coronary occlusion and those of the second type are least vulnerable. Furthermore, intercoronary anastomoses vary in animals. In man, the extent of intercoronary anastomoses is thought to be genetically determined.

Certain epidemiologic population studies now being planned or actually underway should bring us some useful information concerning the relative importance of heredity. Such a study is that of a comparison of the amount of serum cholesterol and the prevalence of important degrees of coronary atherosclerosis in Irishmen living in Greater Boston and in their brothers living in Ireland. The ideal study, even in only a few such couples, would be a similar comparison of identical twin males.

One should also refer to the infants who die of coronary heart disease due to left ventricular myocardial necrosis from the lack of oxygen in the blood supplied by the left coronary artery congenitally arising from the pulmonary artery; this is more likely, however, to be due to a fault in vascular development during fetal life than to an inherited defect.

As helpful illustrations of hundreds of my own patients who apparently inherited the liability to coronary heart disease I shall cite several cases.

#### Case 1

Mrs. L.D., aged 52, a successful, driving business woman, still overweight despite a recent loss of 17 pounds, with a serum cholesterol of 360 mg. per cent. Diagnosis: Coronary heart disease, angina pectoris 3 months previously, and coronary thrombosis 6 weeks previously. In her family her brother had had coronary heart disease

and died at 63 of a bleeding peptic ulcer; her mother is living and well at 83, but 3 paternal aunts all died at about 60 of coronary heart trouble.

Thus, this middle-aged woman had undoubtedly inherited from her father's side of the family a "tendency" to coronary heart disease.

#### Case 2

Mr. W.S., aged 40, married, educator. Present weight 178 with a height of 69 inches—a drop of 25 pounds in 4 years by diet. Serum cholesterol 325 mg. per cent. Diagnosis: Hypertension for 8 years, coronary heart disease, neurocirculatory asthenia, angina pectoris on effort for 6 years since the age of 34, and coronary thrombosis twice, on present occasion and 4 years earlier at 36. Family history showed that his father had coronary thrombosis first in his 40's and died of a second attack at 56; a grandfather died of coronary heart trouble in his 60's.

#### Case 3

Mr. O.B., aged 42, newspaper publisher. Weight 175 pounds, which is 20 pounds heavier than in his younger days, at a height of 69 inches. Serum cholesterol 280 mg. per cent. Diagnosis: Coronary heart disease with recent coronary thrombosis and questionable coronary thrombosis 3 years earlier. In the family history, the father died at 57 of coronary heart disease, as did also one uncle at 46, and 2 other uncles (twins) at 63.

He was obviously a candidate from the standpoint of family history alone.

#### Case 4

S.G., aged 38, executive. Weight 180 pounds 3 years previously, now 160 after dieting. Diagnosis: Coronary heart disease, myocardial infarction twice, 3 years and 1 year previously, and mild diabetes. Family history revealed that his father had died at 49 of coronary thrombosis, that his mother was living and well, and that a grandfather had been diabetic.

#### Case 5

J.F., aged 42, congressman. Diagnosis: Acute myocardial infarction with pericarditis. Family history showed that his father died at 66 of "heart trouble" and his mother at 48 of coronary heart disease.

#### Case 6

C.F., aged 40, executive. Diagnosis: Acute myocardial infarction, posterior in position, 1 month previously. Family history revealed that his father died at 57 of angina pectoris, his mother at 65 of cancer, and a grandfather of heart disease at an age unspecified.

**Case 7**

J.C.H., aged 41, cotton broker. Diagnosis: Acute coronary thrombosis. Family history revealed that his father died a cardiac death at 54, and his mother of a "stroke."

In conclusion, it has been clinically evident that heart disease due to serious coronary atherosclerosis does "run in families" and that there are other inherited characteristics such as a high serum cholesterol, mesomorphic body build, diabetes, and atherosclerosis in other arterial systems. The mechanism by which this inheritance occurs is still a mystery. It is very important that the practicing physician as well as the investigator pay more attention to the family histories of his coronary patients and, as a matter of fact, to the younger, especially male, still healthy members, of the families already affected at older ages. But as Dr. Page has also pointed out and as I would reiterate now, there is definitely hope for the future not only for those who are candidates for coronary heart disease but for many others, if we can initiate and maintain an adequate measure of both basic and applied research in the field of human genetics.

**Summario in Interlingua**

Le rolo del hereditate in le pathogenese de morbo cardiac coronari es tanto importante como currenemente negligite. Il es a sperar que illo va esser investigate tanto intenseamente como on investiga in nostre dies le rolo de factores ambiental in le pathogenese de morbo coronari. Le medico de practica general cognosce le evidentia del predisposition genetic pro morbo cardiac coronari, sed a fin que iste evidentia deveni le thema de recereas scientific, le medico practic debe facer se recereator o obtener le assistentia de un nove generation de novemente orientate geneticos.

Le complexitate del biochimia del hereditate es illustrate per plure citationes. Le facto del hereditabilitate de morbo cardiac coronari es illustrate per un numero de breve historias de casos.

Le mecanismo per que iste hereditabilitate functiona remane mysteriose. A causa de isto, il es importantissime que le medico practic (como etiam le investigator scientific) presta plus attention al al historias clinic del familias del pacientes coronari individual. Il es etiam importante-forsan plus importante ancora-que le medico practic se occupa del juvene non-coronari membros de familias in que membros de etates plus matur ha morite ab morbo cardiac coronari o suffre currenemente de illo.

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# Pathologic Physiology of Angina Pectoris and Acute Myocardial Infarction

By HERRMAN L. BLUMGART, M.D., AND PAUL M. ZOLL, M. D.

**T**HE DISTRESS or pain of angina pectoris and of acute myocardial infarction is consequent to ischemia. In angina pectoris the ischemia is transitory because of temporary disproportion between the blood supply and the myocardial requirements; in acute myocardial infarction the ischemia is prolonged and leads to the irreversible changes of necrosis. The actual stimulus at the nerve end-organs that give rise to the pain has not been identified with certainty. Sir Thomas Lewis termed it the "P factor." It has certain characteristics in common with lactic acid: it is acid, is destroyed by alkali and by oxidation, and develops most rapidly under oxygen deprivation and carbon dioxide accumulation.

The predisposing cause of these two conditions is coronary obstruction. Atherosclerosis is the most prevalent lesion. Syphilitic aortitis distorting the coronary ostia and rheumatic arteritis are next in frequency. Rarely, periarteritis nodosa, scleroderma, amyloid, hemorrhagic diseases, vegetations of bacterial endocarditis or tumors impinging on the ostia, emboli, and the arteritis associated with systemic infections may be responsible. Congenital malformations and trauma are sometimes encountered. The chief effect of these lesions is to interfere with coronary blood flow and to prevent an adequate blood supply to the myocardium.

Various factors greatly influence the degree of ischemia. Among these are the anatomic distribution of the coronary arteries, the localization of the atheromatous lesions

and the rates of development of the lesions, and the compensatory collateral channels.

## Anatomic Pattern of the Coronary Arteries: the Incidence and Localization of Arterial Occlusions

The 3 main coronary arterial branches, the left anterior descending, the left circumflex, and the right coronary vary from heart to heart in the relative size of the area they supply. Schlesinger classified hearts in 3 groups according to the anatomic distribution of these 3 arteries.<sup>1</sup> In group I, comprising half the hearts in his series, the right coronary artery predominated in the blood supply of the heart, nourishing the right ventricle and a large part of the posterior wall of the left ventricle. In group II, comprising approximately one third of human hearts, the coronary artery blood supply was balanced between the right and left coronary arteries. The right coronary artery supplied the right ventricle plus the posterior wall of the interventricular septum, and the left coronary artery supplied the left ventricle plus the anterior part of the interventricular septum. In group III, comprising one sixth of human hearts, the left coronary artery predominated and supplied more than the entire left ventricle and interventricular septum. In some instances the left coronary artery extended to the free surface of the right ventricle. There are various degrees of this preponderance of the left coronary artery. In the least marked form both the right coronary artery and the left circumflex coronary artery extend to the crux of the heart, and both terminate in parallel posterior descending branches. In other hearts the terminal branch of the left circumflex coronary artery constitutes the sole posterior descending coronary artery.

There is no great sex difference in the distribution of the groups although women evi-

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dently have a somewhat disproportionately large number of the balanced group II hearts.

The degree to which these anatomic groups are hereditary and may be responsible for familial tendencies to myocardial infarction and angina pectoris is unknown.

Another variation in local anatomy of the coronary arteries that may significantly influence the effects of coronary occlusion is the presence or absence of a coronary artery to the area of the conus arteriosus (conus artery).<sup>2</sup> The coronary vessel supplying this area may arise as a branch of the right coronary artery or as a separate, third, supernumerary coronary artery with its own ostium from the aorta. Because of its separate origin the conus artery is independent of obstruction so often found at or near the mouth of the right coronary artery. The conus artery also appears particularly suited as a collateral source of blood supply to the heart. Its direct communication with the aorta and its location between the main left descending and right coronary arteries make it a ready source of anastomotic connection between the aorta and the coronary arterial system distal to the zones in which the incidence of occlusion is highest. Furthermore, the low incidence of occlusions in the conus artery, lower than in the other coronary arteries, enhances its value as an effective pathway of collateral blood supply.

The presence of a large, third division of the left coronary artery was described in the Bantu and suggested by Brink as an explanation for the low incidence of angina pectoris and myocardial infarction in that race.<sup>3</sup> Although the presence of this racial anatomic variation has been confirmed, it is not associated with significant anastomotic circulation between the left and right coronary arteries and does not appear to be of primary importance in the lowered incidence of clinical manifestations of coronary disease in this race.<sup>4</sup>

#### **Pathologic Characteristics of Coronary Arteriosclerosis**

Coronary artery occlusions are limited to the 3 main coronary arteries and their pri-

mary branches, and are almost entirely epicardial. The highest incidence of occlusions is not directly at the mouth of the vessel but a short distance distal to the mouth.<sup>5</sup> One half are within 3 cm. and 70 per cent are within 4 cm. of the coronary ostia. The lesions are mostly localized and segmental. In a study of almost 200 occlusions of the main coronary arteries and their branches in a series of 400 hearts, 64 per cent were less than 5 mm. in length and 40 per cent were less than 3 mm. in length. More than half of all the occlusions were in the main stems; the remainder were in the primary branches. Fibrosis and calcification may involve not only the intima but also the entire media. Occlusions in affected hearts tend to be multiple. In 100 consecutive hearts with occlusions, there were 248 occlusions or an average of 2.5 occlusions per heart. Only 33 of these hearts had but 1 occlusion.

Atherosclerotic narrowing or occlusion of a coronary artery may be caused by an atheroma with progressive fibrosis, by a superimposed thrombus, by intramural hemorrhage in an atheroma, or by rupture of an atheromatous abscess. Thus, in 6,800 consecutive autopsies, thrombosis on an arteriosclerotic basis (43 per cent), occlusions due to arteriosclerosis per se (41 per cent), and intramural hemorrhage (8 per cent) presumably on an arteriosclerotic basis made up 92 per cent of the causes of occlusion, with the remaining 8 per cent distributed among embolism, inflammation, and syphilis.<sup>6</sup>

The arteries are metabolically active structures that may be altered even in the absence of atherosclerosis. They participate, as do other tissues, in the aging process. The media, initially made up of circular, smooth muscle and elastic fibers, and the adventitia, a meshwork of connective tissue containing elastic fibers, both lose elastic fibers with age. These changes are most rapid in the left anterior descending artery and slowest in the right coronary artery. Fibroelastic changes occur in the intima and media, atrophy of the smooth muscle is seen in the media, and irregular patches of connective tissue develop.

### Comparison of Blood Supply to Skeletal and Cardiac Muscle

The circulation of the heart presents many interesting differences from the rest of the body. Skeletal muscle on vigorous contraction can increase its oxygen consumption 30 or more times. This vastly increased requirement is met in part by an increase in arterial and capillary blood flow and in part by greater extraction of oxygen from each unit of blood passing through the capillaries. Thus, the oxygen content of venous blood, which is approximately 12 volumes per 100 ml. with skeletal muscle at rest, may be reduced to 5 volumes per cent or less on exercise. This ability to borrow on the "reserve" oxygen is not enjoyed by the heart. Under normal conditions the venous blood of the coronary sinus contains only 2 to 5 volumes per cent of oxygen. There is little to borrow and so the heart must "pay as it goes" by increasing the coronary arterial blood flow proportionately when the myocardium needs more oxygen to do more work. Skeletal muscle is also different in that it can continue to contract during exercise, even if the oxygen supply is momentarily inadequate, by incurring an oxygen debt which is repaid later during rest. The myocardium, however, cannot do this; it depends for its contractility on the oxygen immediately available in the coronary blood. It ceases to contract when it has incurred only one fifth of the oxygen debt skeletal muscle can endure.

Skeletal and cardiac muscle also present an interesting difference in their vascular supply. The smaller arteries and arterioles of striated muscle communicate freely with each other by large anastomotic vessels. Except for sudden occlusion of large trunks such as the brachial, iliac, or femoral arteries, infarction of skeletal muscle is rare. The coronary arteries, on the other hand, are end arteries in a physiologic or functional sense. It has gradually become the consensus that the connections that exist *normally* among the coronary arteries are only fine communications of an arteriolar or capillary nature, which are less than  $40\mu$  in diameter. These inter-

communications, while of some limited functional value, are not sufficient to prevent infarction of the myocardium when coronary arteries are ligated experimentally in animals or are suddenly occluded by thrombi or emboli in man.<sup>7, 8</sup>

Obviously, therefore, anatomic patency of the coronary arteries is of cardinal importance in the maintenance of normal cardiac nutrition and performance. The very large extraction of available oxygen by the normal heart, the inability of the myocardium to incur a sizable oxygen debt, and the fact that coronary arteries are functional end arteries in the normal heart make it necessary that any significant increase in oxygen need by the heart be met by an increase in coronary blood flow.

Failure to meet the demands of the myocardium as a whole may lead to congestive heart failure; ischemia of certain areas may lead to the clinical symptom of cardiac pain or disturbances of impulse formation and conduction in the form of arrhythmias; if the ischemia is sustained, actual injury or necrosis of heart muscle, i.e., myocardial infarction, may develop.

### Effect of Acute Coronary Occlusion

When a coronary artery is suddenly and completely occluded in a previously normal heart, a myocardial infarct is usually produced. This sequence is observed experimentally and clinically. The coronary arteries consequently must be considered to be end arteries in the physiologic sense.<sup>8</sup> The size of the infarct, however, is always less than the total territory supplied by the artery.<sup>9</sup> This difference is related to the fact that minute intercoronary capillary and arteriolar connections less than  $40\mu$  in diameter are normally present. These may be readily demonstrated in the normal heart upon injection of a colored watery solution into a coronary artery by its immediate appearance in other areas of the heart that are supplied by the other coronary arteries. The peripheral border of the infarcted muscle may be supplied by blood oozing through these fine channels

or, as Wiggers maintained, by diffusion from the surrounding myocardium.

Within a minute following acute occlusion myocardial contraction diminishes progressively as ischemia continues. As the contractions become feeble, they are balanced by the intraventricular pressure, and the ischemic area expands paradoxically with each systole.<sup>7, 8</sup> The small collateral channels that normally exist in the coronary arterial system do not supply enough blood to support useful contractions for many minutes.

In an extensive study of 1,200 human hearts, the clinical manifestations were interpreted on the basis of the findings disclosed by the Schlesinger technic. By this technic, the coronary arterial system is injected with a lead-agar suspension which penetrates regularly as far as 40  $\mu$  in diameter. Only the larger intercoronary communications that have been demonstrated to be functionally important are delineated by this method.

In 9 per cent of normal human hearts, larger intercoronary communications, 40  $\mu$  or larger, may be observed.<sup>10</sup> They are not sufficiently numerous to prevent infarction; however, clinical, electrocardiographic, and pathologic data indicate that the heart may recover without structural damage if the duration and degree of ischemia are not too great. Experimentally, myocardial ischemia produced by temporary occlusion of the main stem of a coronary artery for 40 minutes generally produces areas of irreversible damage and necrosis.<sup>11</sup> At any time during or after occlusion, ventricular fibrillation or other arrhythmias may appear. Their development may well be related to differences in the gradient of oxygen potential.

#### **Effect of Gradual Coronary Occlusion: Importance of Intercoronary Arterial Anastomoses**

In human hearts with old occlusions, intercoronary collateral channels of a size greater than 40  $\mu$  were observed in practically 100 per cent of cases. These collateral vessels served as a bypass or detour and supplied the myocardium distal to the area of marked narrowing or occlusion from neighboring un-

occluded arteries. This anastomotic circulation evidently develops as a compensatory phenomenon in relation to marked arterial narrowing or occlusion.

These phenomena have been reproduced by the authors under controlled experimental conditions in the domestic pig, the coronary arterial tree of which is strikingly similar to that of man.<sup>12</sup> Intercoronary collateral channels of more than 40  $\mu$  may be seen within 24 hours after marked coronary narrowing but their rich development usually requires 7 to 21 days. After 5 to 12 days of preliminary narrowing, sudden acute occlusion of the narrowed artery no longer regularly results in death. Examination of the myocardium grossly and microscopically showed that these collateral channels not only permitted survival of the animal but at times protected the myocardium from serious damage. Somewhat similar results in dogs have been reported by others.<sup>13, 14</sup> Under favorable conditions the major portion of the coronary artery system can be gradually occluded with minimal or no infarction in the animals that survive.

The clinical counterpart of these experiences, i.e., the occurrence of complete coronary artery occlusions without myocardial infarction has been noted repeatedly.<sup>15</sup> In a small series, Snow and his associates<sup>16</sup> also observed gross infarction to be smaller than anticipated but they encountered no instance of complete occlusion without infarction. There is general agreement, however, regarding the prevalence of functionally important anastomotic channels in response to coronary arterial obstruction and their great protective value against myocardial damage.

In contrast to this general agreement regarding the development of extensive collateral channels in hearts with marked coronary narrowing and complete occlusion, divergent results have been reported regarding the incidence of sizable, functionally significant intercoronary anastomoses in the normal heart. In an extensive series of over 1,500 consecutive normal hearts studied by the Schlesinger technic, the incidence of

anastomoses was 9 per cent after exclusion of anemia, cardiac hypertrophy, valvular heart disease, and other categories in which hypoxia evidently leads to an increased incidence of anastomoses.<sup>10</sup> Although this experience has been confirmed by many others<sup>9, 17</sup> certain observers using other techniques have reported an incidence greater than 10 per cent. Laurie and Woods,<sup>18</sup> indeed, alone among investigators, observed sizable intercoronary arterial anastomoses in 75 per cent of patients over 40 years of age and in only 23 per cent of patients with severe atherosclerosis.<sup>18</sup> There is reason to believe that the role of anemia and technical differences in pursuing the study account for their aberrant results.<sup>4, 10, 19</sup>

The development of intercoronary collateral vessels also can be demonstrated experimentally by measurement of retrograde flow and pressure from a severed main coronary branch. Immediately following abrupt occlusion of a main coronary branch, the retrograde coronary flow approximates 5 to 5.8 ml. per minute compared to control values of 2 to 3 ml. per minute and is relatively constant in any one dog for a few hours.<sup>7</sup> Measurements of retrograde flow during temporary clamping of the other coronary arteries indicate that the latter are the major source of flow.

After long-continued obstruction of a coronary artery or a branch in an otherwise normal animal heart, the flow of blood from the cannulated end of the artery becomes quite large. It begins to increase within a few hours, may double within 2 days, and may become 3 to 4 times the control level within a week. Within a few weeks, the flows approximate the values for the normal rate of inflow before occlusion in that coronary artery or branch. The observation that the retrograde blood had the same content of oxygen and carbon dioxide as that in a systemic artery leaves no doubt that the collateral circulation is on the arterial side of the coronary capillary bed. The gradual augmentation of retrograde flow is attended by similar elevations of systolic and diastolic

pressures in the peripheral end of the occluded coronary artery.

Observations of the heart post mortem in man are in accordance with these experimental studies and explain the apparent inconsistency between the presence of long-standing obstructive lesions, on the one hand, and the absence or relatively slight pathologic or clinical evidence of myocardial damage, on the other hand. Indeed the hearts of patients with angina pectoris may show one or more occlusions in 2 or even 3 main stems, a rich collateral development, and only scattered myocardial fibrosis.<sup>20, 21</sup> While there is a general relationship between the incidence of coronary occlusion and the occurrence of angina pectoris, other modifying factors such as the exact site of the occlusion, the importance of the vessel involved, the adequacy of the collateral circulation, the rate at which such occlusions or narrowings develop, the temporary influence of emotion, exertion, and vasomotor reflexes are also of great importance. Although damage to the heart is minimized by the development of the collateral circulation, the margin of safety or, as it may be termed, "the coronary reserve" is reduced.

#### Augmentation of Coronary Blood Flow by Medical Measures

Augmentation of the coronary collateral circulation beyond that occurring naturally following marked coronary narrowing or complete obstruction inevitably is limited because the extent of the natural development appears to be well nigh maximal and marked in the area where it is most effective. Vasodilator drugs have not been demonstrated to accelerate the rate of development or augment the extent of the intercoronary anastomoses.<sup>22</sup> In grossly normal hearts from anemic patients the incidence of anastomoses was 39 per cent compared to 9 per cent in grossly normal hearts from nonanemic patients.<sup>10, 19</sup> Anemia may conceivably have some therapeutic application in the treatment of coronary artery disease but its application seems hazardous and to date its practical use has not been feasible.

Augmentation of the coronary collateral circulation after a program of exercise has been observed experimentally by Eckstein after coronary occlusion in the dog.<sup>23</sup> Although the clinical implications are important, they do not afford a therapeutic approach of major proportions. Furthermore, exercise in dogs with coronary artery occlusions was attended by increased risk of myocardial damage and death.<sup>23</sup> It is a plausible assumption that relative anoxia is the factor that stimulates the formation of the collateral circulation after coronary obstruction, in anemia, exercise, cardiac hypertrophy, and cor pulmonale.<sup>10, 22</sup>

#### The Question of Vasomotor Control of the Coronary Circulation

"Spasm" of the coronary arteries with diminished blood flow has also been invoked frequently to explain the precipitation of episodes of angina pectoris. Attacks of angina brought on by exposure to cold or "by a disturbance of mind"<sup>24</sup> and prevented or terminated by nitroglycerin are difficult to explain solely on the basis of long-standing anatomic changes in the coronary arteries or myocardium. Spasm could result from a direct effect of epinephrine or other circulating substances on the smooth muscle of the arteries, or it could be induced by vasomotor reflex impulses. The vast accumulation of experimental observations of coronary vasoconstriction in animals cannot be transposed to man with assurance, but recent observations in patients with angina pectoris now afford strong evidence of the existence and significance of vasomotor influences. Vasomotor reflex changes account in part at least for the effects on anginal attacks of atropine, local chilling, and anesthesia of the hands, carotid sinus stimulation, tobacco smoking, pulmonary emboli, and gastrointestinal disorders. Indeed, reflex coronary vasomotor spasm may be important in increasing the extent of myocardial necrosis and the mortality following acute coronary artery occlusion.<sup>25</sup>

The existence of vasomotor effects that reduce coronary flow is in no way incompatible

with the demonstration and importance of widespread pathologic changes in the hearts of patients with angina pectoris. The primary etiologic factors of coronary obstruction, valvular disease, and arterial hypertension are not to be considered the exclusive cause of cardiac pain; rather they constitute the stage upon which various transitory precipitating factors may operate. Thus, coronary vasoconstriction, anemia, tachycardia, fever, hypermetabolism, or hypotension may act as precipitating agents in the production of pain in a patient whose coronary circulation is already compromised by arterial obstruction. In the absence of an adequate pathologic substrate, these factors rarely, if ever, are sufficient in themselves to produce angina pectoris. In a series of 1,200 patients studied clinically and at postmortem examination by injection of the coronary arteries not a single instance was found of angina pectoris in the absence of structural heart disease.<sup>21</sup>

#### Summary

Some of the unique physiologic characteristics of the coronary circulation have been pointed out. In the normal heart, the coronary arteries are *functionally* end arteries. Watery injections, however, reveal anatomic fine anastomotic communications between the coronary arteries measuring less than 40  $\mu$ . But they are of limited functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion. Complete occlusion or considerable narrowing of one or more coronary arteries may exist without giving rise to any clinical signs or symptoms and without having produced myocardial damage. The apparent inconsistency between the presence of long-standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage is dispelled by the demonstration of a collateral circulation which serves as a by-pass in relation to the obstruction in each of these hearts. The pathologic and physiologic substrates of angina pectoris, coronary failure, and acute myocardial infarction have been discussed.

### Summario in Interlingua

Es signalate certes del distinctive characteristics del circulation coronari. In le corde normal, le arterias coronari es—ab le puncto de vista de lor function—arterias terminal. Tamen, injectiones aquose revela le presentia anatomic de finissime communicationes anastomotice inter le arterias coronari. Le diametros de iste communicationes es minus que 40  $\mu$ . Illos es de signification functional, a grados restrinbite, in tanto que illos servi a obviar le adverse effectos de un subite constriction o occlusion coronari. Le complete occlusion o un restriction considerabile de un o plures del arterias coronari pote exister sin ocasionar ulle signo o symptoma e sin provocar ulle injuria myocardial. Le apparente paradoxo del presentia possibile, durante prolongate periodos de tempore, de obstructive lesiones arterial sin ulle resultante evidientia pathologic o clinic de injuria myocardial es resolvite per le demonstration de un circulation collateral que servi como detorno con respecto al sito del obstruction in tal cordes. Le substratos pathologic e physiologic de angina de pectore, disfallimento coronari, e acute infarction myocardial es discutite.

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## SPECIAL ARTICLE

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### Treatment of Hypertensive Disease

By N. N. SAVITZKI, M.D., AND V. P. NIKITIN

**O**F THE variety of pathologic conditions involving abnormally high blood pressure, one is of outstanding importance—essential hypertension. According to current views, the principal pathogenetic mechanism responsible for elevation of blood pressure is assumed to be a generalized arteriolar spasm, with a resulting rise of peripheral resistance to the outflow of blood. It has been proved by our investigations, however, that such a concept is far from being universally acceptable.

Not infrequently, the elevation of blood pressure is due to a disturbance of coordination between functions of various links of the cardiovascular system. We have ample evidence that an inadequate response of arterioles (insufficient dilatation) to increasing cardiac output, rather than arteriolar spasm, may be the direct cause of blood pressure elevation. In the treatment of patients with hypertensive disease, the use of potent vasodilating drugs proves to be of minor importance, success depending on a judicious combination of various therapeutic measures aimed at the restitution of normal cardiovascular function. Treatment should include a set of procedures, attacking the causative factors of the disease. The course of the process, as well as the patient's individuality are to be taken into consideration in selecting a suitable combination of therapeutic agents. Thus, it is well known that there may be wide variations in the sensitivity of individual patients to hypotensive agents having central, ganglionic blocking, adrenolytic, or myotropic activities. It would therefore be a

mistake to recommend a "unified" method of treatment, suitable in any case of hypertensive disease.

There do exist, however, important general conditions, that are essential for efficient prophylaxis and treatment of hypertension. Among these may be mentioned the organization on a nationwide scale of outpatient services responsible for the management of patients (termed dispensary system), treatment in overnight or daytime sanatoria attached to factories or institutions, availability of sanatoria and health resorts, and creation of favorable occupational and living conditions.<sup>1-4</sup>

In this communication no attempt is made to give a general review of current methods of treatment for hypertensive disease. Only some data are discussed on which information seems to be scarce outside our country.

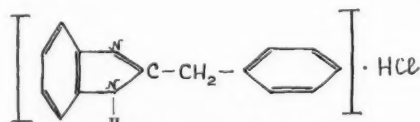
Prolongation of natural sleep has been used extensively as a means of restoring disturbed function of neurohumoral controlling systems. Experience supports our opinion that favorable effects are not attained by high dosage of sedatives, tending to produce signs of intoxication. Besides, it would not conform to the principle of protective inhibition, implying a reduced excitability of nervous cells.

Accordingly, we have been using low doses of barbiturates with a medium duration of activity (Noctal, Nembutal, Medinal, etc.). Barbiturates are generally taken twice daily: before the midday meal and before retiring. In some cases, sedatives should be taken in the morning. In this way, the duration of normal sleep can be prolonged to 12 or 13, occasionally

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as long as 16 hours a day. It has been shown by L. P. Ivanov<sup>5</sup> that such treatment causes no signs of toxicity and does not affect basal metabolism, nonprotein nitrogen, or blood indican, and prothrombin. Protracted pharmacologic sleep has a beneficial effect upon the general well-being of patients, bringing about alleviation of headaches and of precordial pain. In many cases, the favorable influence of protracted sleep can hardly be attributed to a marked hypertensive effect. It tends to bring about a normal state of higher nervous activity, to improve the blood supply of tissues, and to overcome regional circulatory disorders. A number of different methods of sleep therapy has been suggested; they are reviewed in well-known monographs.<sup>1, 2, 6</sup> The effectiveness of the method rises, when used in combination with vasodilating agents. These are particularly desirable for patients having frequent regional vascular spasms.

On a suggestion from S. V. Anitchkov,<sup>7</sup> an original preparation synthesized in the Soviet Union, dibazole (2-benzyl-benzimidazole chloral hydrate)



has been submitted to clinical trials.

Dibazole has a papaverine-like action. It was found to reduce blood pressure on subcutaneous, as well as intravenous, administration to animals following total destruction of the central nervous system. Dibazole was shown to suppress spasm of arterial smooth muscle induced by barium chloride and acetylcholine.<sup>7, 8</sup> Unlike papaverine, dibazole displays definite effects on the central nervous system, even at low doses; and it has been used for the treatment of various paralytic or paretic conditions, as well as for sequelae of cerebral injury.<sup>9-11</sup>

At present, our experience is based upon records of routine administration of dibazole to 403 patients with hypertensive disease, (241 women, 162 men). Dibazole treatment has been resorted to at various stages of the hyperten-

sive disease. In all of the patients, treatment was preceded by a period of clinical observation. The group included 84 patients with stage I hypertensive disease, 273 with stage II, and 46 with stage III. Dibazole treatment was continued for 12 to 40 days. Intramuscular or subcutaneous injections of 1 ml. of a 2-per cent solution of dibazole were given every day to 330 patients once, or twice in the more serious cases; 3 oral doses, 0.02 to 0.04 Gm. each, were administered to 73 patients. No undesirable effects of dibazole treatment have been noted.

Dibazole treatment was followed by considerable improvement of general condition and reduction of blood pressure in 250 patients. In the other 153, no significant hypotensive effect could be attained, although most of them found their condition had improved, as they were free of severe headaches, tinnitus, and paroxysms of cardiac distress. Dibazole treatment had no effect in 23 patients with hypertensive disease, stage III. Nine of them died: 7 of progressive renal failure and uremia and 2 of cerebral hemorrhage.

The fact that dibazole relieved symptoms of precordial pain in hypertensive patients as well as data, obtained by I. A. Novikova in the laboratory of Professor N. A. Kharauzov,<sup>12</sup> on suppression of experimental atherosclerosis by dibazole, led to a trial of this agent in patients with atherosclerotic cardiosclerosis accompanied by severe anginal pain and in patients with myocardial infarction at the stage known as "recovery period." Systematic dibazole treatment was found to bring about gradual relief or disappearance of anginal pain. A single injection of dibazole proved ineffective for controlling an acute episode.

Interesting features of circulatory dynamics under the influence of dibazole were revealed in a study by V. I. Kuznetsov et al.<sup>13, 14</sup> Detailed data on variations of arterial pressure were available as oscillographic records obtained by means of a special instrument—the mechanocardiograph. Its design provides the possibility of obtaining a high-speed oscillographic record during compression of a blood

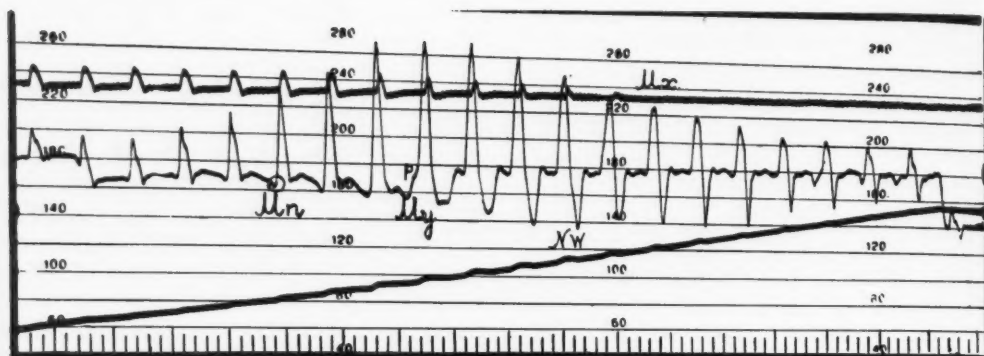


Figure 1

*Tachyscillograph. Mn, minimal pressure; My, mean dynamic pressure; Nw, piezometric pressure; Mx, final or maximal pressure.*

vessel. A method for the interpretation of these records has been elaborated.<sup>15, 16</sup> The tachymetric oscillogram (tachyscillogram) assumes a very characteristic appearance, deformation of the basal part of the tracing providing a fairly accurate estimate of the level of arterial pressure (fig. 1). The value of minimal pressure (Mn) is indicated as the moment at which the first diastolic notch appears on the lower section of the tracing. Mean dynamic pressure (My) is determined by the appearance of a closure wave (p) in the lower section of the systolic rise. True systolic, or piezometric pressure (Nw), corresponds to the moment of the largest negative oscillation. An abrupt decrease of amplitude of negative deflections and disappearance of pulsation, recorded simultaneously from the radial artery, indicates the level of final or maximal pressure. The difference between maximal and piezometric pressure depends on the magnitude of hemodynamic impact ( $Mx - Nw$ ), so that the force of impact pressure is readily obtained by subtraction.

In the majority of cases a single 1-ml. injection of a 2-per cent solution of dibazole is followed by a decrease of the maximal and, somewhat less, of the systolic pressure. As a result the magnitude of hemodynamic impact diminishes. Mean and minimal pressures remain almost unaltered, as here oscillations are generally within 5 to 10 mm. Hg (table 1).

In addition to tachyscillographic investigations, research on various aspects of the activity of dibazole under clinical conditions was based on a number of tests: basal metabolic rate (Krogh), arteriovenous oxygen difference (actylene method), computation of cardiac output (minute volume), specific peripheral resistance (obligate, actual, working value), work of the heart (obligate and actual). Data from a series of examinations by V. I. Kuznetsov<sup>13</sup> are given as an illustration (table 2).

As a rule, administration of dibazole was followed by an increase of the arteriovenous difference, while oxygen consumption per unit time was not altered. The increase of the arteriovenous difference may be assumed to be due to dilatation of capillaries and opening of additional canals. The latter results in a reduced velocity of blood flow through tissues and increases oxygen consumption. The diminished cardiac output (minute volume), without any significant reduction of the stroke volume should be considered as an adjustment, tending to relieve the strain of the heart's work. Computation of the actual work performed by the left ventricle provides convincing evidence of the relief afforded to the heart muscle by an injection of dibazole (table 3).

Thus, the favorable therapeutic effect of dibazole is mainly determined by its capacity to relieve the heart muscle, to raise oxygen

consumption by tissues, and to abolish regional spasms. These data provide some explanation for the benefit derived by patients with frequently recurring paroxysms of stenocardia from systematic dibazole injections.

Alterations of circulatory dynamics, similar to those due to dibazole, were found to follow subcutaneous administration of phenatin (1 ml. of a 5 per cent solution). Phenatin, a product of condensation of amphetamine and nicotinic acid, stimulates the central nervous system, but in contradistinction to amphetamine, it has a hypotensive effect.

Data on the treatment of hypertensive disease with ganglionic-blocking agents ("Pendiomid" — diethylenetriamine; hexamethonium salts; Nanophynum and others)\* as well as Rauwolfia serpentina alkaloids, may be omitted due to space limitations; considering the number of available publications, research on this aspect seems to be widely known.

A judiciously planned diet is highly important for the success of therapy in hypertensive disease. The benefit of a salt-free diet has long been established by clinical practice.<sup>17, 18</sup> Dysfunction of the pituitary-adrenal system in hypertensive disease often results in enhanced mineralo-corticoid activity with retention of sodium and chloride in tissues and extracellular fluid and depletion of potassium ions. Naturally, a number of special rations has been suggested for compensating disturbances of mineral metabolism in hypertension. Kempner's rice diet seems to be the more widely known. It should be noted, however, that such a diet is tolerated with difficulty due to its monotony and poor taste, many patients refusing to submit to this treatment.

We have been using a so-called "potassium diet" since 1955. It contains vegetables, fruits, sugar, melted butter, sour cream, saltless bread, peas, beans, oatmeal, rice, and jam, providing a total of 2,329 to 2,313 calories. The amount of sodium in the ration is 0.334 to 0.664 Gm.; of potassium 4.462 to 3.774 Gm.; the Na:K ratio being 1:10 or 1:6. The potas-

Table 1

*Effects of Dibazole on Tachyscillogram in Four Patients*

Patient, age in years	Time (min.) after Dibazole*	Mn	Arterial pressure			
			My	Nw	Mx	S
S., 36	Control	115	140	175	210	35
	10	118	145	180	202	22
	20	110	150	185	200	15
	30	110	150	180	195	15
	40	110	145	180	205	25
Sh., 30	Control	105	122	140	165	25
	10	105	122	145	165	20
	20	100	125	140	160	20
	30	100	120	140	155	15
	40	100	120	140	155	15
D., 71	Control	93	100	155	192	37
	10	90	100	150	175	25
	20	70	95	137	162	25
	30	75	94	140	160	20
	40	75	94	140	160	20
P., 45	Control	130	150	195	240	45
	10	120	150	195	240	45
	20	110	145	195	230	35
	30	110	140	195	220	25
	40	105	140	182	195	13

\*1 ml. of 2% dibazole.

Mn, minimum pressure; My, mean dynamic pressure; Nw, piezometric pressure; Mx, final or maximal pressure; S, impact pressure (Mx-Nw).

sium diet is maintained for 14 or 15 days. Daily urinary elimination of chlorides may be reduced to 0.3 to 0.5 Gm. The hypotensive effect begins to appear as early as when daily chloride elimination has been reduced to 2.5 to 2.0 Gm.

The results of clinical trials have proved this diet to be an effective therapeutic method in hypertensive disease. Its use is indicated, along with various hypotensive agents, in the treatment of patients with persistent elevation of blood pressure (fig. 2).

It should be noted that in occasional cases the hypotensive effect of the potassium diet proves to be much greater than that of continuous administration of such undoubtedly potent agents as the Rauwolfia alkaloids (fig. 3). Favorable results have been obtained in the treatment of hypertensive disease by other authors using diets based on closely related principles.<sup>18, 19</sup>

\*A preparation of lower toxicity—"Benzohexonium"—is used now in the Soviet Union.

Table 2

*Hemodynamic Effects of Dibazole*

Patient	Condition at time of examination	Arterio-venous difference	Output/minute volume/ml.			Systolic volume	O <sub>2</sub> consumption per minute
			Acetylene test	Obligate	Per cent difference		
T-v	Resting	83.7	3440	4880	-20	50	288
	Dibazole	84.6	3405	4880	-30	50	288
S-a	Resting	74.3	2665	3327	-20	35	198
	Dibazole	80.0	2475	3327	-26	41	198
P-a	Resting	51.3	3275	3000	+ 3.2	55	168
	Dibazole	56.0	3000	3000	0	55	168
V-a	Resting	58.7	3525	3277	+ 7.6	58	207
	Dibazole	62.3	3323	3277	+ 1.4	55	207
Y-u	Resting	55.1	3757	3280	+15.2	47	207
	Dibazole	59.1	3510	3280	+ 7.0	50	207
M-n	Resting	55.7	4112	3900	+ 5.4	67	234
	Dibazole	59.2	3953	3900	+ 1.4	63	234
W-s	Resting	61.8	4223	4313	- 2.1	64	261
	Dibazole	60.9	4286	4313	- 0.6	65	261
K-o	Resting	56.6	4252	4140	+ 2.7	74	252
	Dibazole	67.1	3756	4140	- 9.3	63	252
J-o	Resting	51.0	4763	4178	+14.0	72	243
	Dibazole	56.2	4324	4178	+ 3.5	70	243
A-a	Resting	63.9	3083	3283	- 6.1	49	207
	Dibazole	71.4	2900	3283	-11.7	47	207

Table 3

*Effects of Dibazole on Cardiac Work*

Patient	Condition at time of examination	Work of the heart, Kg./min.		
		Obligate	Actual	Per cent difference
S-a	Resting	2.7	4.0	48
	Dibazole		3.7	47
V-a	Resting	2.6	4.1	58
	Dibazole		3.8	46
M-n	Resting	3.1	4.3	38
	Dibazole		3.9	22
Sh-t	Resting	2.3	3.5	52
	Dibazole		2.7	17
K-o	Resting	3.3	3.6	+ 9
	Dibazole		2.9	-12

In our opinion failure to obtain any effect from rest and pharmacologic agents is to be regarded as an indication for prescribing the potassium diet, over-nutrition being a relative indication.

Before closing, it should be emphasized, with regret, that a very simple, although fairly effective method—oxygen inhalation—has not become a routine method of treatment in hypertensive disease. Investigations of arterial blood saturation and respiratory activity in patients with hypertensive disease have disclosed slight arterial hypoxemia in half of the

cases.<sup>20, 21</sup> Arterial hypoxemia was detected in patients with hypertensive disease, stage I, though it was more pronounced and of more frequent occurrence in stage II. In these cases, the oxygen capacity of hemoglobin was unimpaired and the dissociation curve of oxyhemoglobin was normal. Carbon dioxide tension of arterial blood remained at a normal level, or somewhat lower. Studies of pulmonary ventilation proved its effectiveness to be unimpaired, while alveolar air oxygen tension was normal, or even slightly higher, in these patients. It should be noted that in patients with hypertensive disease, alterations of the respiration quotient, vital capacity, limit and reserve of respiration are by no means rare. The occurrence of arterial hypoxemia at an early stage of hypertensive disease is evidently due to a disturbance of adequate relationship between pulmonary ventilation and circulation. At later stages of the disease, there may be an additional factor—impaired diffusion capacity of respiratory membranes.

In hypertensive disease, oxygen therapy improves the well-being of patients. Pulse and respiration rates are lowered, dyspnea is relieved, and there is a marked hypotensive

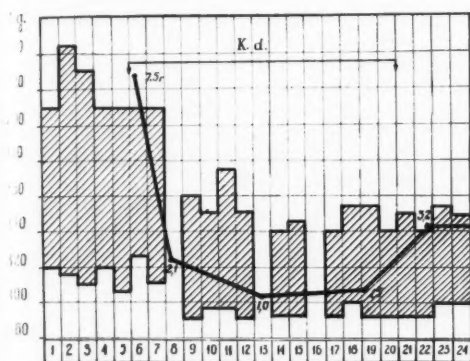


Figure 2

Patient B, age 50. Hypertensive disease, stage II. Blood pressure dynamics and chloride elimination on potassium diet.

effect. Inhalation of air with high oxygen content (40 to 50 per cent) at regularly spaced intervals in an oxygen tent has often been found to reduce blood pressure to normal levels for more or less considerable periods.

In conclusion, it is stressed that the aim of therapeutic procedures is to promote restitution of normal functioning of neuro-humoral mechanisms and normal tissue metabolism. Wide variations in the responses of patients to hypotensive agents may indicate the variety of pathogenic mechanisms underlying the presenting symptom of the disease, elevated blood pressure.

#### Summario in Interlingua

Es presentate un revista del tractamento de hypertension essential como illo es practicate in le U.R.S.S. Le autor sublinea le necessitate de differentiar le tractamento secundo le idiosyncrasyas del patiente individual.

Inter le valide principios general, le effecto benefice es notate que le prolongation del somnio exerce super le hypertension e le stato general del sanitate del patiente hypertensive. Le prolongation del somnio pote esser effectuate sin risco per medios pharmacologic.

Es reportate in detalio le successos clinic obtenite in le U.R.S.S. per medio del recentemente synthetizate droga cognoscite como dibazol (hydrato de 2-benzyl-benzimidazol-chloral). Le effecto de dibazol super le dynamica circulatori esseva studiate per medio del mechanocardiographo que provide rapidissime registrationes oscillographic del vasos sanguinee sub compression.

Circulation, Volume XXII, August 1960

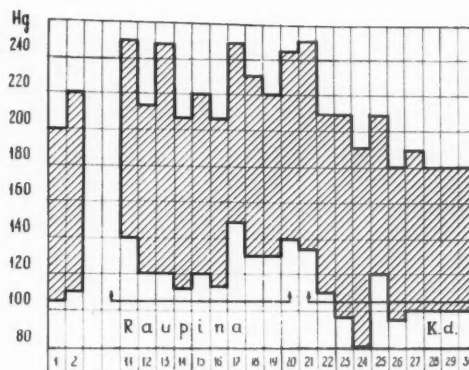


Figure 3

Patient V, age 47. Hypertensive disease, stage II. Absence of hypotensive effect of Rauwolfia alkaloids; blood pressure reduced on potassium diet.

Es notate le vapor de un "dieta a kalium" in le regime de patientes con hypertension.

Le autor regretta que cursos de inhalation de 40 a 50 pro cento de oxygeno non es utilisate plus extensamente in le tractamento de hypertension. Ille reporta su successos therapeutic effectuate per medio de iste methodo e presenta un breve explication physiologic del benefice effectos de illo.

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Symposium on Coronary Heart Disease  
Will Be Continued in the September 1960 Issue

## CLINICAL PROGRESS

### Dissecting Aneurysm of the Aorta The Clinical Features of Thirty Autopsied Cases

By BLAIR D. ERB, M.D., AND I. FRANK TULLIS, M.D.

**I**N RECENT years the diagnosis of dissecting aneurysm of the aorta has undergone a transition in significance. Formerly, this entity was considered a rather hopeless but academically interesting phenomenon. Today, however, with the growth of experimental and clinical vascular surgery, the diagnosis of dissecting aneurysm of the aorta has become a necessity from a practical and therapeutic standpoint. Already the successful surgical management has been reported from several centers.<sup>1-4</sup> A distinct increase in the natural survival rate of 10 per cent<sup>5</sup> cannot be expected, however, unless the frequency of antemortem diagnosis is increased. The incidence of antemortem diagnosis has been reported from Domzalski's 0 per cent<sup>6</sup> to Logue's 83 1/3 per cent,<sup>7</sup> but in major series the average incidence appears to be between 30 and 50 per cent, and this rate appeared only after the monograph by Shennan in 1934.<sup>8</sup> Only 27 per cent of the 30 autopsied cases at the John Gaston Hospital in the last 10 years were diagnosed ante mortem. It is the purpose of this paper to review the clinical experiences with dissecting aneurysm of the aorta in autopsied cases at the John Gaston Hospital in the last 10 years, with emphasis on the appearance of the patient and associated conditions.

Historically Morgagni<sup>9</sup> in 1760, Maunoir in 1802,<sup>10</sup> and Laennec in 1826<sup>11</sup> described the lesion in the aorta, and Pennock<sup>12</sup> in 1839, and Peacock<sup>13</sup> in 1843 gave our knowledge the

foundation for the first correct antemortem diagnosis reported in 1855 by Swaine and Latham.<sup>14</sup> Further progress in clinical concepts was slow, however, until Erdheim's description of medionecrosis.<sup>15</sup> Only 6 cases had been diagnosed prior to Shennan's analysis of 300 cases in 1934, but since that time the entity has been recognized with increasing frequency. Interestingly, King George II was reported<sup>16, 17</sup> to have died of aortic dissection while straining at stool.

#### Incidence

The actual incidence of dissecting aneurysm has not been determined but it appears to be a more common process than originally thought. The literature through 1947 was reviewed by Levinson and co-workers,<sup>18</sup> who could find only 734 cases. In the literature through 1957, we found an additional 682 cases, and with the 30 presented here the total in the literature is approximately 1,416 cases.

The autopsy incidence has varied between 1 per 745<sup>19</sup> and 1 per 70.<sup>20</sup> The latter series, however, was a report of coroner's cases in which the incidence of sudden unexpected death is higher than in the usual hospital series. In the past 10 years at John Gaston Hospital 30 cases have been found among 9,280 autopsies, an incidence of 1 per 309. In a collection of series in which the figures were given<sup>18, 21-25</sup> there were 151 cases in 46,869 autopsies, an incidence of 1 per 310 autopsies.

The age range is variable but many aortic dissections have been reported in children and 1 was found in a 14-month-old child.<sup>26</sup> One case was reported at 100 years of age<sup>8</sup> and 3 of our patients were 85 years old. It appears

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to be most common, however, in the fifth and sixth decades, but as many as 24 per cent have been reported under the age of 40.<sup>27</sup> In our series the age ranged from 36 years to 85 years, with an average age of 56 years. Only 3 were under 40 years of age. Men generally predominate 2 to 1.<sup>8</sup> In our series there were 20 men and 10 women, again 2 to 1. There appears to be a slightly higher incidence in the American Negro than in Caucasians,<sup>18, 22</sup> and only 1 Chinese has been reported.<sup>18</sup> In our series 24 were Negro and 6 were Caucasian, an equal incidence in relation to our admission ratio.

#### Pathology

A dissecting aneurysm of the aorta is a hemorrhage in the aortic media with separation of the layers of the aortic wall. This may or may not be associated with an intimal tear, which most commonly occurs in the ascending aorta just distal to the aortic valves. The tear may occur at the great vessels in the aortic arch or in the descending or the abdominal aorta. Grossly the aorta presents a definite but variable increase in external size and is usually saccular or fusiform in shape. The clinical manifestations usually are a function of the site of the aortic tear and the extent of the dissection. Although the medial hemorrhage usually extends peripherally, proximal dissection may occur, often terminating, as is reported in 78 per cent of one series,<sup>27</sup> with rupture into the pericardial sac and cardiac tamponade as the cause of death. Ruptures into the pleural space (usually the left), into the retroperitoneal space, or into the esophagus<sup>28</sup> have been reported as causes of death, but "re-entry" of the dissecting hematoma into the original aortic lumen may occur, giving rise to the "double-barrelled" aorta, which often is compatible with many years of useful life. Occlusion of branches of the aorta may cause death secondary to the affected organ or system.

Histologically a focal degenerative process, cystic medionecrosis, is seen within the media. Gore<sup>29, 30</sup> described 2 types of medionecrosis, 1 of which usually occurs under the age of 40,

consisting predominantly of elastic fiber degeneration, and the other occurs in the older age group in which muscle fiber degeneration predominates. Erdheim's original description reported rarefaction of the media, absence of external elastic laminae, muscle atrophy with cystic spaces between irregularly branching fibers, and slight thickening of the intima.

Cystic medionecrosis may be due to disease of the vasa vasorum<sup>31-33</sup> and Gore<sup>34</sup> thought that rupture of the thin-walled friable vasa vasorum caused intramural hemorrhage that ruptured the intima. The pressure of the systolic blood flow then may cause extension of the dissection down the loosely connected media.

#### Etiology and Associated Conditions

There are certain conditions clinically associated with dissecting aneurysm of the aorta that may aid in establishing the diagnosis. Most outstanding is the Marfan's syndrome, characterized by abnormally long and thin extremities, fingers, and toes, with relaxation of the ligaments, hypotonic musculature, dolichocephalic head, kyphosis, funnel-chest, subluxation of the lenses, high-arched and sometimes cleft palate, and prominent ears.<sup>35-37</sup> Pulmonary anomalies are reported.<sup>38</sup> Other congenital cardiovascular anomalies are seen in the Marfan's syndrome.<sup>39</sup> The familial incidence of Marfan's syndrome suggests some hereditary aspect of dissecting aneurysm. Variants of the Marfan's syndrome occur and any of the many characteristics may be present. Two of the patients in this series exhibited the clinical findings of the Marfan's syndrome.

An increased frequency of dissecting aneurysm has been reported with pregnancy.<sup>27, 40, 41</sup> Of the 49 women reported in 1 series under 40 years of age,<sup>27</sup> 24 (or 50 per cent) were associated with pregnancy. This appears to be more common in the last trimester<sup>40</sup> but occurrence during the postpartum period is noted. There was 1 woman, a Negro aged 33, in this series who was 2 weeks postpartum.

The frequent association of hypertension with dissecting aneurysm is well known but its exact role remains open to question. It may

provide the driving force for medial dissection once the intimal tear occurs. The role of atherosclerosis is even more nebulous, and the earlier concept of disturbed nutrition of the media through atherosclerosis has not been well substantiated.

Coarctation of the aorta enhances the possibility of medionecrosis and dissecting aneurysm.<sup>42</sup> Medionecrosis is usually found proximal to the coarcted segment,<sup>43</sup> presumably due to increased intraluminal pressures. One case of complete aortic atresia at the usual site of adult coarctation with dissection has been reported.<sup>44</sup>

Recently McKusick<sup>45</sup> reported 4 cases of dissecting aneurysm associated with aortic stenosis, and cystic medionecrosis was present in all cases. Other cases have subsequently placed increased emphasis on this associated lesion,<sup>46-48</sup> and Heath, Edwards, and Smith<sup>48</sup> offered the explanation that the high velocity jet of blood passing the aortic valves strikes the more slowly moving blood distally, causing a lateral displacement of force which then results in structural fatigue and possibly medionecrosis.

The role of trauma has been suggested but is unclear.<sup>49-52</sup> Trauma even in the form of a fishbone in the esophagus has been considered responsible for dissection.<sup>53</sup> Hypothyroidism has been suggested as a preexisting causative factor,<sup>54, 55</sup> and it has even been proposed that the high incidence of dissecting aneurysm during pregnancy may be due to failure of the thyroid gland to undergo its physiologic hyperplasia.<sup>56</sup> Although 1 of our cases had had a thyroidectomy 17 years before her dissection, a relationship of thyroid function to aortic dissection has not been established.

It is generally agreed that syphilis is not an etiologic factor in aortic dissection.<sup>17</sup> It has been suggested that syphilis hinders the development of aortic dissection by scarring of the media.<sup>57</sup> A history of syphilis or positive serology was found in 10 of our 30 cases but no lesions of cardiovascular syphilis were seen.

Aortic dissection also has been reported in giant cell aortitis,<sup>58, 59</sup> in tuberculous aortitis,<sup>60</sup> due to translumbar aortography,<sup>61</sup> associated

with ganglionic blocking drugs,<sup>62, 63</sup> ergotamine tartrate,<sup>64</sup> and even cortisone acetate in hamsters.<sup>65</sup> The role of an experimental diet of *Lathyrus odoratus* (sweet pea) in the production of dissecting aneurysm in rats has been found,<sup>66-68</sup> and the toxic principle appears to be B-aminopropionitrile.<sup>69</sup>

#### Clinical Features

An entity which has frustrated so many physicians obviously would be the subject of many different schemes of classification. One such classification is based on duration of survival.<sup>18</sup> The acute type terminates fatally within 24 to 48 hours; the subacute type may be more gradual, persisting for a period of days or weeks, and the chronic or "healed" type may survive for months or years. We prefer, however, a classification based on the clinical features and the appearance of the patient, as modified from Domzalski,<sup>6</sup> Warren and McGowan,<sup>25</sup> or Baer.<sup>70</sup> We include 6 groups of manifestations: cardiac, peripheral arterial, pulmonary, abdominal, renal, and neurologic. The involvement of several systems may be the first diagnostic lead.

#### Presenting Complaint

Pain was the presenting complaint in 21 or 70 per cent of our patients, in the chest in 12, abdomen in 5, and extremities in 4. Baer reported that 51 per cent of 86 patients had pain<sup>70</sup> and Levinson and associates<sup>18</sup> reported pain in 78 per cent of 58 cases, but in only 29 per cent was it in the chest. The chest pain characteristically was described as sudden, substernal, radiating through to the back, penetrating "gas-like," sharp, squeezing, crushing, tearing, and smothering. It occasionally radiated to the jaw, the shoulders, or the arms. The onset characteristically was sudden and in several instances was related to exertion, e.g., chopping wood, painting from a ladder, and so forth. In several instances the pain was described as being at the peak of intensity at the onset. This has been considered of major importance in differentiating this entity from acute myocardial infarction, in which pain gradually becomes more severe.<sup>71</sup> The pain also frequently radiates into the abdomen and

midpigastrium. It must be remembered that silent dissection may occur without any pain or, on the other hand, the general condition of the patient is such that an adequate history cannot be obtained.

Abdominal or epigastric pain was also of sudden onset, severe, radiating to the back, colicky, constant or intermittent, vise-like, tearing; and the patient characteristically had difficulty in localizing the exact point within the epigastrium.

Pain in the extremities represented a symptom of arterial occlusion. Coldness, numbness, tingling, and weakness in the affected extremity also were mentioned.

Five patients (17 per cent) were admitted as neurologic or psychiatric problems. One patient, a 47-year-old man with Marfan's syndrome, was admitted to the psychiatric service for despondency and depression of recent onset. A murmur had been described approximately 1 year previously. The course was progressively downhill, with development of congestive failure, renal failure, and recurrent hemothorax. At postmortem examination a chronic "healed" dissecting aneurysm was found. Four patients (13 per cent) were admitted with strokes, 2 with right and 2 with left hemiplegia.

Three patients (10 per cent) were admitted with longstanding congestive heart failure and died of intractable failure. This is not uncommon in the chronic dissection when re-entry has taken place.

One patient was admitted to the orthopedic service after a fall. A small dissection of the abdominal aorta was found at autopsy but death was due to pulmonary embolus.

Secondary complaints included dyspnea, vomiting, hemoptysis, edema, apprehension, pleuritic pain, epigastric distress, sweating, syncope, polyuria, hematuria, cough, and weakness.

The general appearance of the patient as one who is suffering a catastrophe may give the initial lead. Twenty-three of our patients (77 per cent) were acutely ill; 12 presented as acute cardiovascular episodes (see table 1). Four were admitted to the surgical service as

problems of peripheral arterial occlusion, and 3 were considered to be patients with acute surgical abdomens.

#### Cardiac Manifestations

Hypertension or heart disease existed in 21 patients (70 per cent) and hypertension by history or examination was present in 16. Tachycardia was noted in 19 cases. Not infrequently the patient appeared to be in clinical shock but the blood pressure was elevated. Cardiomegaly was found in 19 cases (63 per cent).

Cardiac murmurs, particularly if known to be of recent origin, are of diagnostic importance (table 2). An aortic diastolic murmur has been classically found in dissecting aneurysm when the ascending aorta is involved. This murmur has occurred in from none<sup>6</sup> to 56.2 per cent<sup>72</sup> in different series, but in a larger series 28 per cent had aortic diastolic murmurs,<sup>18</sup> similar to our incidence of 27 per cent (table 3). We wish to call attention to the high incidence of aortic systolic murmurs found both in Levinson's and in our series. Aortic murmurs, systolic, diastolic, or both, occurred in 41 per cent of the 2 series.

The cause of these murmurs has been the subject of much dispute. It has been suggested that leakage of blood through the intimal tear produces the murmur.<sup>73</sup> Others considered that the medial hematoma distorts the aortic valve ring, resulting in insufficiency of the valve.<sup>18, 74, 75</sup> It is also possible that a transverse tear in the intima near the aortic commissure loosens the intimal support for the cusp, allowing sagging of the cusp in the direction of the ventricle and insufficiency of the valve.<sup>76</sup> It is likely that several mechanisms may produce the murmur and that they may vary in different cases. The existence of murmurs is very important for the diagnosis and in establishing the extent of the process. Our percentage of antemortem diagnosis closely parallels the percentage of murmurs of aortic insufficiency.

Friction rubs of pericardial origin usually are considered rare in dissecting aneurysm and none was encountered in our series. How-

Table 1

*Apparent System Involved from General Appearance and Initial Impression in Thirty Cases at John Gaston Hospital*

Apparent system involved	Number of cases	Per cent
Acute catastrophic C-V episode	12	40
A. With peripheral artery occlusion	3	
B. Without peripheral artery occlusion	9	
Central nervous system (stroke)	4	13
Peripheral artery embolism (only)	4	13
Acute surgical abdomen	3	10
Chronic congestive heart failure	3	10
Chronic renal disease with uremia	2	7
Psychiatric problem	1	3
Orthopedic problem (trauma)	1	3

ever, in 505 autopsied cases of Hirst, Johns, and Kime<sup>77</sup> friction rubs were found in 22, or 4 per cent.

Cardiac tamponade often occurs from rupture of the aneurysm into the pericardial sac. As most dissections begin in the ascending aorta, the proximity of the tear to the pericardial reflection would explain the high incidence of rupture into the pericardial sac (78 per cent) in 1 series.<sup>27</sup> Pericardial aspiration may be diagnostic as well as therapeutic.<sup>77</sup>

#### Peripheral Arterial Manifestations

Occlusion of the peripheral arteries often results from the engorged dissecting hematoma and the peripheral arteries may give a number of interesting signs. A significant difference in blood pressure between 2 extremities is characteristic. In our series pulses in some peripheral arteries were absent in 13, not remarkable in 5, and were not examined in 12. "Migratory" or transient arterial occlusion may occur<sup>78,79</sup> and delay in the pulse beat in the peripheral arteries<sup>8</sup> and reduplication of the carotid pulse have been seen.<sup>80</sup> Pulsation in either sternoclavicular joint has been described<sup>81</sup> and tenderness below a dissecting aneurysm is known as the Weissbosman sign.<sup>82</sup>

#### Extracardiac Manifestations in the Chest

These include dyspnea, cough, hemoptysis, pleural pain, and pleural effusion or hemothorax. Most commonly the pleural effusion

Table 2

*Summary of the Murmurs Described in Thirty Cases of Dissecting Aneurysm of the Aorta at John Gaston Hospital Compared with the Murmurs Described by Levinson et al. in Fifty-eight Cases from Los Angeles County Hospital<sup>18</sup>*

Type of murmur	This series (30 cases)	Levinson's series (58 cases)	Total (88 cases)
Aortic systolic only	6	3	9
Aortic diastolic only	3	5	8
Apical systolic only	4	9	13
Apical diastolic only	1	0	1
Aortic systolic and aortic diastolic	3	8	11
Apical systolic and aortic diastolic	2	0	2
Aortic diastolic and systolic and apical systolic	0	3	3
Apical systolic and apical diastolic	0	1	1
Aortic systolic and apical systolic	0	3	3
No murmurs heard	9	26	35
Not evaluated	2	0	2
Total in which murmurs were heard	19	32	51

is on the left. The mistaken diagnosis of pneumonia, malignant disease, or pulmonary infarction is not uncommon. One of the patients in this series with hemothorax had 9 thoracenteses, 4 of which contained atypical cells, but at autopsy no malignant disease was found.

#### Abdominal Manifestations

The most common abdominal manifestation is the history of pain, but hematemesis,<sup>83</sup> melena,<sup>84</sup> distention of the sigmoid suggesting obstruction,<sup>83</sup> and volvulus<sup>85</sup> may be seen. Cholecystitis<sup>86</sup> and pancreatitis<sup>84</sup> are often suspected. Three of our patients were admitted to the surgical service for suspected acute surgical conditions of the abdomen, suggestive of cholecystitis. No abdominal operations were done, however.

#### Renal Manifestations

Involvement of the kidneys may result from aortic obstruction proximal to the renal arteries or by dissection of the renal arteries,<sup>87</sup> and is manifested by flank pain, hematuria, and uremia. Occasionally ureteral calculus is suspected, and the distribution of flank pain

Table 3

*Summary of Aortic Murmurs Described in Thirty Cases in This Series and in Levinson's Series<sup>18</sup> of Fifty-eight Cases. Nineteen of All Cases had Both Aortic Systolic and Aortic Diastolic Murmurs*

Murmurs	This series (30 cases)	Levinson's series (58 cases)	Total (88 cases)	Per cent of cases
Aortic murmurs	14	22	36	41
Systolic	9	17	26	30
Diastolic	8	16	24	28

may be especially confusing when hematuria exists. Four of our patients had hematuria but only 1 had gross hematuria.

#### Neurologic Manifestations

These interesting findings have been classified as arising from ischemic necrosis of the peripheral nerves, ischemic necrosis of the spinal cord, and ischemic necrosis of the brain.<sup>88</sup> Ischemic necrosis of the peripheral nerves is the most common neurologic finding and is manifested by numbness, coldness, or tingling. Peripheral sensory loss and areflexia may exist. When the spinal cord is involved, flaccid areflexic paraplegia, hypesthesia, and atony of the bladder may occur, with sphincter paralysis.<sup>89</sup> The most striking neurologic finding, however, is ischemic necrosis of the brain due to carotid artery occlusion, with flaccid hemiplegia, hemianesthesia, and often coma. Four of our patients presented this picture. Neurologic changes may be transient.

#### Laboratory, Electrocardiographic, and Roentgenographic Findings

Laboratory data were obtained in 27 of our 30 patients. The hematocrit levels varied between 30 and 59 volumes per cent and a mild anemia was present in 10 patients. Leukocytosis was found in 21 patients, usually of a moderate degree, and in all but 2 it was less than 20,000 white blood cells per cubic millimeter. Hematuria was noted in 4 patients and was gross in 1 instance. Azotemia was present in 16 patients but only 3 had nonprotein nitrogen values above 100 mg. per cent. Serum

amylase was normal in both instances in which it was determined. The serum glutamic oxaloacetic transaminase was examined in 1 case and was elevated (88 units) but there was electrocardiographic evidence of acute posterior wall myocardial infarction.

#### Electrocardiographic Features

The electrocardiographic findings are variable but in 20 patients on whom tracings were obtained, 16 were abnormal; however, non-specific changes in the ST-T segments were frequently seen. Changes suggestive of acute myocardial infarction were found in 5 patients. The diagnosis of dissecting aneurysm might well be overlooked in these patients. The pattern of acute myocardial infarction might be the result of extension of the process into and involving the coronary arteries<sup>90</sup> or due to occlusion of the coronary ostia by the dissecting hematoma.<sup>91</sup>

Other abnormal electrocardiographic findings in our series included disturbances in rhythm (atrial fibrillation, wandering atrial pacemaker, and extrasystoles), disturbances in conduction (first-degree atrioventricular block, complete and incomplete left bundle-branch block) and left ventricular hypertrophy.

#### Roentgenographic Features

The roentgenographic appearance of a dissecting aneurysm depends upon the location of the dissecting process. The most common features have been thoroughly outlined by Lodwick.<sup>92</sup> Wood, Pendergrass, and Ostrum in 1932 reported widening of the supracardiac shadow, with deformity, and thought that a shadow visible along the innominate artery indicated extension along that vessel.<sup>93</sup> They also described tracheal deviation, due either to the aneurysm itself or to fluid in the left pleural space. As a rule, however, the most common finding is straightening of the aortic curvature, occasionally with rough irregularities.<sup>94</sup> Repeated films may indicate daily extension of the process, and a chest film prior to the dissection is important for comparison.<sup>95</sup> Lodwick also described different density in the aorta, particularly when the dissection in

olved only the lateral portion of the aorta. The widened aortic wall may appear more radiolucent than the dense central core of the aorta. Not infrequently, in the age group most commonly associated with dissecting aneurysm, calcified intimal plaques are found. When dissection occurs, the calcified intima may be pushed medially and the adventitia may be widened laterally. Widening of the space between calcified intima and lateral aortic shadow may be diagnostic. The normal aortic wall measures 2 to 3 mm. in width and measurements of greater than 3 to 5 mm. are suggestive, and of more than 1.0 cm. are practically diagnostic of this condition.<sup>92, 95</sup>

Left ventricular hypertrophy is frequently present and signs of pericardial effusion may be noted. Pleural fluid is frequently seen on x-ray, most commonly in the left pleural space.

Special roentgenographic procedures have been recommended. The right posterior oblique position has been suggested as most satisfactory on conventional x-ray studies.<sup>94</sup> Fluoroscopy may reveal absence of aortic pulsations<sup>92</sup> or in the case of hemopericardium, absent or diminished cardiac pulsations. Roentgenograms with a barium-filled esophagus may be helpful.<sup>92</sup> Angiocardiography has been reported to be useful.<sup>96, 97</sup> One case was diagnosed by translumbar aortography when the radiopaque medium extended an unusual distance cephalad, and was associated with paradoxical visualization of the iliac vessels.<sup>98</sup> This procedure, however, is not recommended. Laminograms have been said to be most helpful in the older age groups with the most arteriosclerotic changes.<sup>99</sup> For evaluation of abdominal dissecting aneurysms, Lodwick recommended retroperitoneal and intraperitoneal air injections to furnish a radiolucent background.<sup>92</sup>

Of our 30 cases 19 had roentgenographic studies. Only 1, however, was thought to be diagnostic of dissecting aneurysm but 6 others (32 per cent) were suggestive of aortic aneurysm. In an additional 6 the heart revealed varying degrees of enlargement and the aorta

was reported as "elongated and tortuous." Pleural effusion was seen in 3 patients.

#### Treatment

With the advent of newer surgical techniques dissecting aneurysm of the aorta has become a "surgical disease." Since the prognosis is related to re-entry of the dissecting sac into the original aortic lumen,<sup>100</sup> the surgical approach is directed toward producing a natural "cure" and has been described as the "re-entry procedure."<sup>74, 101, 102</sup> The surgical management was first attempted by Gurin et al.<sup>103</sup> in 1935, and later by Shaw in 1955.<sup>104</sup> Both were unsuccessful in that the patients died with renal failure, but re-entry was accomplished. DeBakey et al.<sup>4, 102</sup> devised a successful approach which attempts to prevent further dissection, restore blood flow, and either to remove or to repair the lesion. The type of repair depends on the site of the intimal tear. When the aortic arch is involved, re-entry with obliteration of the false passage below is chosen. When the intimal tear is distal to the arch, the lesion is excised and replacement graft is installed. Some modifications have been suggested by others.<sup>105</sup>

The preoperative management may be life-saving; absolute bedrest with relief of pain by opiates is mandatory. Oxygen should be used for impending shock or dyspnea. Careful regulation of severe hypertension with ganglionic-blocking drugs may help prevent rupture of the aneurysm.<sup>106</sup> When signs of peripheral vascular occlusions are present, the limb should be kept in a horizontal position at room temperature, and a sympathetic block may be helpful.<sup>107</sup>

#### Summary

The clinical diagnosis of dissecting aneurysm of the aorta depends on awareness of the entity, keen clinical suspicion, and an understanding of the varied manifestations. Clinical suspicion is sharpened by association of certain preexisting conditions found to be related to an increased incidence of aortic dissection. Recognition of the Marfan's syndrome, pregnancy, or preexisting hypertension in a patient presenting as an acute catastrophe

may lead to the diagnosis. A family history of aortic dissection is similarly helpful.

The variable manifestations call for careful reasoning. Multiple system involvement in many cases is the initial lead in establishing the diagnosis. The many systems frequently involved in the symptomatology of aortic dissection have in common the origin of the blood supply. When the aorta is damaged, branches to various organs may be affected so that the symptoms depend on the branches involved. Because any portion of the aorta may be involved in the dissecting process, no single clinical picture suffices for its recognition. Aortic valvular findings often are seen with involvement of the ascending aorta, central neurologic findings may result from occlusion of the carotid arteries, spinal cord manifestations may result from occlusion of the intercostal arteries, renal manifestations may be seen with renal artery involvement, and so on down the aorta. However, the pattern of a catastrophic episode—whether cardiovascular, neurologic, or abdominal—calls for consideration of aortic dissection. All of the finesse of the most careful physical examination may be required to make the diagnosis but the co-existence of chest pain, aortic murmurs, and peripheral artery occlusion is practically diagnostic. Laboratory adjuncts including roentgenographic evidence of mediastinal widening, evidence of hematuria, and the absence of electrocardiographic evidence of myocardial infarction may be helpful. Electrocardiographic evidence suggestive of myocardial infarction does not, however, exclude aortic dissection.

Dissecting aneurysm of the aorta now is a surgical emergency that requires early accurate diagnosis and early surgical treatment, if the natural survival rate of 10 per cent is to be improved.

#### Summario in Interlingua

Le diagnose clinic de aneurysma dissecante del aorta depende de un alerte e acute suspicion clinic e del precise comprehension del varie manifestationes que characterisa iste entitate. Le suspicion clinic es augmentate per le presentia de un complexo de pre-existente conditiones pro le quales un augmentate incidencia de dissection aortic ha essite constatate. Le

recognition del syndrome de Marfan, de pregnantia, o de hypertension pre-existente in un patiente presentate con un catastrophe acute pote esser le base del diagnose. Un historia familial de dissection aortic es similimente de valor.

Le variabilitate del manifestationes impone le necessitate de un precise rationamento. Affectiones plurisystemal es frequentemente le prime indicio in supporto del diagnose. Le varie systemas que es frequentemente concernite in le symptomatologia de dissection aortic es interrelationate per le communitate de lor provision de sanguine. Quando le aorta es lesionate, su brancas ducente verso varie organos pote esser implicate a varie grados, de maniera que le symptomatas depende de qual brancas del aorta es afficite. Viste que non importa qual portion del aorta pote esser le victima del processo de dissection, nulle specific e unic tableau clinic suffice como base de su recognition. Symptomatas in le valvula aortic es frequente quando le aorta ascendente es implicate; manifestationes in le systema nervose central pote esser le resultado de un occlusion del arterias carotidic; occlusion del arterias intercostal pote esser responsabile pro symptomatas referibile al medulla dorsal; manifestationes renal occorre in consequentia de un affection del arterias renal; e assi successivamente usque al fin del aorta. In omne caso, le occurrentia de un episodio catastrophie—sia cardiovascular, sia neurologic, sia abdominal—demanda que dissection aortic es prendite in consideration. Omne le raffinamento del plus meticulose examine physic es frequentemente necessari pro le obtention del diagnose, sed le co-existencia de dolores thoracic, murmures aortic, e occlusion de arteria peripheric es practicemente infallibile como prova de dissection aortic. Constatationes laboratorial qu es a vices de valor include le observation roentgenologic de un allargamento mediastinal, le establimento de hematuria, e le prova que le electrocardiogramma exhibi nulle indicio de infarcimento myocardial. Tamen, le presentia de indicios electrocardiographic de infarcimento myocardial non exclude le possibilitate de dissection aortic.

In nostre dies, aneurysma dissecante del aorta representa un situation de urgentia chirurgic que require un prompte e accurate diagnose e le precoce intervention operatori si nos desira meliorar le cifra del superviventia natural que amonta a 10 pro cento.

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## ABSTRACTS

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### ATHEROSCLEROSIS

**Berkowitz, D., Likoff, W., and Sklaroff, D.M.:**  
**The Effect of Sitosterol on Radioactive Fat**  
**Absorption Patterns.** *Am. J. Cardiol.* 4: 282  
(Sept.), 1959.

The administration of a single 30-ml. dose of sitosterol (Cytellin) or of 45 ml. daily for periods of 4 to 6 months was found not to change the enteric absorption curve of radioactive triolein in 15 patients with coronary atherosclerosis and an elevated serum cholesterol and in 5 healthy individuals, all on normal diets. Serum cholesterol values in the chronically treated group showed no striking changes.

ROGERS

**Carlson, L. A., and Pernow, B.: Studies on Blood Lipids during Exercise. I. Arterial and Venous Plasma Concentrations of Unesterified Fatty Acids.** *J. Lab. & Clin. Med.* 53: 833 (June), 1959.

The effect of muscular work on unesterified fatty acids (UFA) in man was studied by determining plasma concentrations in arterial blood and femoral veins at rest and during exercise to the point of exhaustion of the exercising leg. Six healthy subjects were studied. The exercising legs extracted UFA from plasma, and the arterial plasma concentration decreased or remained fairly constant during exercise, increasing again during a resting period of 30 minutes. The method is described in detail. The differences in concentration between the arterial and venous blood indicate that UFA were extracted from the blood perfusing the exercising leg at the different work loads up to the maximal. At rest the arterial and venous hematocrit values were

equal, but during exercise they sometimes differed, with the venous values at times 1 to 5 per cent higher than the arterial. In discussing the findings in relation to the energy metabolism of exercising muscular tissues, the authors find support for the theory that UFA is one of the major transport forms for fat needed for immediate energy metabolism and that extraction of UFA during exercise may well be due to the metabolism of fatty acids to yield energy via the Krebs cycle.

MAXWELL

**Davies, D. F.: A Comparison of Erythrocyte and Chylomicron Electrophoretic Migration Times and Serum Cholesterol Levels in Atheroma.** *Clin. Sc.* 18: 263, 1959.

The serum cholesterol was compared with the erythrocyte migration time in patients with and without evidence of coronary artery disease. A close correlation was found between the chylomicron and erythrocyte migration times. The erythrocyte migration time was significantly prolonged in subjects with coronary occlusion compared to a control group. No significant difference was found in this study between the cholesterol level of the coronary group and of the control group; no correlation could be demonstrated between serum cholesterol level and erythrocyte migration time. It is concluded that the migration times are a measure of plasma surface activity and the colloidal stability of plasma fat.

KURLAND

**Gee, D. J., Goldstein, J., Gray, C. H., and Fowler, J. F.: Biosynthesis of Cholesterol in Familial Hypercholesterolaemic Xanthomatosis.** *Brit. M. J.* 2: 341 (Sept. 5), 1959.

Cholesterol is synthesized from acetate units in the body and the mechanism of the biosynthesis of cholesterol in a male patient with familial hypercholesteremic xanthomatosis is the basis of this report. C-labeled acetate was administered orally, and the radioactivity in the free and ester fractions of the plasma cholesterol was estimated at intervals for 144 hours. The specific activity of the free cholesterol reached a maximum within 4 hours, fell relatively rapidly between 4 and 24 hours, and then more slowly. The specific activity of the ester fraction increased slowly and became equal to that of the free cholesterol at about  $2\frac{1}{2}$  days and reached a maximum in 4 days. The results are interpreted as showing an increased rate of biosynthesis of cholesterol from acetate in this patient.

KRAUSE

Malmros, H., and Wigand, G.: **Atherosclerosis and Deficiency of Essential Fatty Acids.** *Lancet* 2: 749 (Nov. 7), 1959.

A method has been devised for producing atherosclerosis in rabbits by feeding a semi-synthetic cholesterol-free diet containing only 8 per cent fat. The cholesterol-free diet without any fat produced a rise in cholesterol and the same aortic changes as in cholesterol-induced atherosclerosis. The effect of various added fats on cholesterol level and aortic atherosclerosis was studied. Milk fat and hydrogenated coconut fat produced hypercholesteremia, and within 3 to 4 months, gross aortic changes. Corn oil and similar oils produced only a small rise in serum cholesterol but no gross aortic lesions. In 1 animal, the fat-free diet was followed by diet with added corn oil; there was a prompt drop in serum cholesterol. This suggests that the hypercholesteremia was due to a deficiency of fatty acids.

KURLAND

### VALVULAR HEART DISEASE

Langer, M., Abelson, D. S., Elkind, A. H., and Kantrowitz, A.: **Massive Hemoptysis in Mitral Stenosis: Control by Emergency Mitral Commissurotomy.** *New England J. Med.* 261: 393 (Aug. 20), 1959.

A 33-year-old man with mitral stenosis developed hemoptysis, which could not be controlled with ordinary measures and which began to reach exanguinating proportions. Dramatic control of bleeding followed an emergency mitral commissurotomy. The authors believe that this patient represents the first reported case of emergency surgical relief of mitral valve obstruction for

the treatment of massive hemoptysis and point out that the operation may be a lifesaving measure in the management of these patients.

SAGALL

Moore, C. B., Kraus, W. L., Dock, D. S., Woodward, E., Jr., and Dexter, L.: **The Relationship between Pulmonary Arterial Pressure and Roentgenographic Appearance in Mitral Stenosis.** *Am. Heart J.* 58: 576 (Oct.), 1959.

Fifty-six adult patients with mitral stenosis subsequently confirmed at surgery were studied by cardiac catheterizations. The findings were correlated with the prominence of the pulmonary arterial segment on the posterior anterior chest x-ray that was defined in terms of the "PA/chest ratio." The latter was determined by dividing the pulmonary arterial size (the distance from the midline, as judged by the thoracic spines, to the edge of the pulmonary arterial segment at its widest point in centimeters) by one half the transthoracic diameter (the greatest transverse diameter of the chest from pleura to pleura in centimeters) and multiplying the result by 100. A positive correlation was found between the "PA/chest ratio" and pulmonary arterial mean pressure. The correlation was exponential in character and resembled the shape of the pressure-volume curve. This correlation was poor in patients with left-to-right shunts and increased pulmonary flow, but in patients with mitral stenosis it proved to be a useful guide to the presence or absence of pulmonary vascular disease without the need for employing cardiac catheterization.

SAGALL

Nolla-Panades, J., Trilla-Sanchez, E., and Balaguer-Vintro, I.: **Phonocardiography in Different Types of Pulmonic Stenosis.** *Cardiologia* 34: 287, 1959.

The phonocardiographic data obtained in 20 patients with pulmonic stenosis are discussed. The most important features in distinguishing isolated stenosis from "tetralogy" were as follows. The intensity of the first sound tended to be louder in the pulmonic area. In no case of pulmonic stenosis was there a systolic click. The peak of the systolic murmur was more delayed in respect to the first sound in pure stenosis. A delayed pulmonary component of the second sound was recorded in all patients with pure pulmonic stenosis and in none with tetralogy. The systolic murmur overlapped the aortic component of the second sound in all patients with pulmonic stenosis. An atrial sound was recorded in all patients

and in half of those with moderate pure stenosis, but in none of those with "tetralogy."

BRACHFELD

**Portheine, H., Bender, F., and Menkhaus, G.: Structural Peculiarities of the Vectorcardiogram in Mitral Stenosis.** *Ztschr. Kreislaufforsch.* 48: 856 (Sept.), 1959.

Vectorcardiograms were registered with the method of Schellong in 36 patients with isolated mitral stenosis confirmed by cardiac catheterization and usually also by operative findings. In 19 patients (type A) the QRS loop was vertical and showed clockwise rotation in the frontal plane; the QR section of the loop had about the same area as the RS section, and the O point and the T loop were situated within the QRS loop. The mean pulmonary artery pressure in this group was 28 mm. In all patients (type B) the frontal QRS loop was similar to type A, but the O point was at the periphery of the loop and the QR area much smaller than the RS area; the T loop was at the left boundary of the QRS loop or outside it. The mean pulmonary pressure in this group was always greater than 26 mm. and on the average 55 mm. Hg. Values of 50 to 78 mm. corresponded to T loops pointing upward and to the left. The right ventricle in this group was usually not dilated according to fluoroscopic findings during catheterization. In 5 patients (type C) the QRS loop was deviated considerably to the right and upward and the R section was undulatory or notched. The T loop pointed to the left and upward or downward. The average mean pulmonary pressure in this group was 47 mm. but the right ventricle usually showed considerable dilatation. The vectorcardiogram can accordingly furnish valuable preoperative information concerning hemodynamic findings in mitral stenosis.

LEPESCHKIN

**Regan, T. J., DeFazio, V., Binak, K., and Hellems, H.K.: Norepinephrine Induced Pulmonary Congestion in Patients with Aortic Valve Regurgitation.** *J. Clin. Invest.* 38: 1564 (Sept.), 1959.

The effects of norepinephrine upon the cardiovascular system in normal subjects were compared with the effects in 8 compensated patients with marked aortic valve regurgitation. Cardiac output, regurgitant flow, and central volume were determined by indicator dye-dilution curves before and during norepinephrine infusions (0.2 µg. per Kg. per minute). Intravascular pressures were recorded from the pulmonary artery and the brachial artery, and a pulmonary capillary tracing was also recorded. The difference in response to

the infusion between the 2 groups was most manifest in the pulmonary capillary and pulmonary artery measurements. In the aortic regurgitation group, a nearly 4-fold rise to levels of pulmonary congestion developed, compared to only a 5 mm. Hg mean rise in the normal group. The slight increase in left ventricular filling pressure in the normal group was associated with a sizable stroke work increase, whereas no significant change in contractility was found in the aortic regurgitation group, despite markedly elevated filling pressures. Bradycardia and increased pulmonary arteriolar resistance, present in the normal group, were absent in the diseased group. It is suggested that displacement of blood from the peripheral venous system was the predominant, if not sole, mechanism in the induction of pulmonary congestion and diminished left ventricular performance during norepinephrine infusions. In 4 patients with aortic regurgitation, the application of tourniquets to induce peripheral venous occlusion resulted in a normal increment in pulmonary capillary pressure and a normal stroke work response to the norepinephrine infusion.

KAYDEN

**Shapiro, H. A., and Weiss, D. R.: Mitral Insufficiency Due to Ruptured Chordae Tendineae Simulating Aortic Stenosis.** *New England J. Med.* 261: 272 (August 6), 1959.

A 39-year-old man, previously in good health, was treated for 3 years for progressive congestive heart failure. The physical findings were those of combined mitral insufficiency and aortic stenosis with the latter considered the dominant lesion. The clinical diagnosis of aortic stenosis was confirmed by an apical heave, a systolic thrill, and the demonstration of a "diamond-shaped" murmur phonocardiographically. The congestive failure was refractory to treatment and became progressively worse. At autopsy the only cardiac lesion was mitral insufficiency secondary to rupture of the 2 chordae tendineae of undetermined cause. It was postulated that a regurgitant jet effect had produced the phonocardiographically confirmed murmur of aortic stenosis.

SAGALL

**Uricchio, J. F., Lehman, J. S., Fitch, E. A., Brest, A. N., Boyer, R. A., and Likoff, W.: The Diagnosis of Traumatic Mitral Regurgitation by Cardiac Ventriculography.** *Am. J. M. Sc.* 238: 73 (July), 1959.

Four cases are described in which mitral regurgitation developed following mitral commissurotomy and in whom left cardiac ventriculography confirmed the presence of significant reflux opacification of the left atrium. Subsequently

in surgery these patients were demonstrated to have had an advanced degree of mitral regurgitation. In these patients, 1 of the leaflets of the valve or some of the chordae tendineae had been ruptured. Although the physical findings may be the same, this technic differentiates the mild and innocuous mitral regurgitation that may develop following commissurotomy from the severe cases. Following ventriculography in these patients there is minimal or no opacification of the left atrium. Cardiac ventriculography thus provides a reliable technic for the differentiation of serious grades of mitral regurgitation following mitral commissurotomy from the benign forms of post-operative mitral incompetence.

SHEPS

### VASCULAR DISEASE

Erskine, J. M., Gerbode, F. L., French, S. W., III, and Hood, R. M.: Surgical Treatment of Thrombotic Occlusion of Aorta and Iliac Arteries. *Arch. Surg.* 79: 85 (July), 1959.

The findings in 33 operated cases of thrombotic occlusion of the aorta and iliac arteries during the period from 1953 through 1957 are reviewed. The symptoms appeared in the middle years of life and were gradually progressive. The majority of patients were men. All had calf claudication, mostly within 1 block; a large majority also had pain in the thigh and hip; impotence, coldness of the feet, leg cramps, and rest pain were also noted. Three patients had heart disease, 2 renal disease, and 2 hypertension. There were no diabetic subjects. Resection and grafting with homografts in most were performed in 82 per cent of the patients; thromboendarterectomy was done in the remainder. In addition to the more definitive procedure lumbar sympathectomy was performed in 60 per cent. One patient developed a hemorrhage and thrombosis at 1 of the iliac anastomoses and required reoperation and regrafting, which finally resulted in gangrene of a toe. In another patient postoperative thrombosis led to infarction of the kidneys, uremia, and death from a cerebral vascular accident. Another man developed chronic uremia in the postoperative period and died 14 months later of serum hepatitis. One patient sustained a cardiac complication in the postoperative period but survived. There were 3 deaths in the follow-up period apparently unrelated to the surgery or to the aorto-iliac disease. The operative mortality, thus, was 3 per cent and the mortality of the entire group was 15 per cent. Immediately after the operation the majority of the patients had strongly palpable pulses down to and including the ankle. During the follow-up period there was some reduction in the number of palpable pulses, especially distally. In the

follow-up period, 37 per cent of 27 patients had no claudication; 3 per cent had some claudication but after greater walking distance than previously; and the remainder had slight or no improvement in walking distance.

SHEPS

Hoye, S. J., Teitelbaum, G. I., and Warren, R.: Atheromatous Embolization: A Factor in Peripheral Gangrene. *New England J. Med.* 261: 128 (July 16), 1959.

The authors reviewed the literature of atheromatous embolization to medium and small arteries of various organs of the body and reported the first case of proved atherosclerotic plaque embolism to cutaneous arteries. In this patient, a 60-year-old man with long-standing hypertension and 3 cerebrovascular accidents in the 4 months preceding his hospital admission, spontaneous pain and darkening of the tips of several toes of both feet developed during the week before hospitalization. The progression of patchy peripheral gangrene, despite prolonged conservative treatment, exploration of the left popliteal artery, and nerve blocks, necessitated bilateral above-the-knee amputation. Pathologic examination of the specimens demonstrated embolic occlusion by atheromatous material of otherwise structurally intact subcutaneous arteries. The source of the emboli in this case presumably was the abdominal aorta and the iliofemoral arteries. It is postulated that cutaneous gangrene from such emboli is more likely to occur in the presence of an arterial circulation already impaired by proximal narrowing of a major artery and, therefore, that operative correction of this narrowing might be advisable in therapy.

SAGALL

LeFevre, F. A., Corbacioglu, C., Humphries, A. W., and deWolfe, V. G.: Management of Arteriosclerosis Obliterans of the Extremities. *J.A.M.A.* 170: 656 (June 6), 1959.

Two procedures, angiography and arterial grafting, have altered the treatment of arterial disease so that now a decision must be made in each patient as to whether or not arterial grafting is indicated. This follow-up study of 500 patients with arteriosclerosis obliterans indicated that about 75 per cent showed little progression of the disease over a 5-year period. All such patients should have benefits of angiographic study to determine the feasibility of arterial grafting. Arteriographic morbidity was 0.1 per cent with no deaths. The effect of sympathectomy on progression in these patients was difficult to assess but in the presence of segmental arteriosclerosis arterial grafting was indicated when technically feasible. All patients with arteriosclerosis oblit-

erans should be diagnosed early and advised of the necessity of strict adherence to good hygiene of the feet, protection from trauma, avoidance of extremes of temperature, and abstinence from tobacco.

KITCHELL

**McCann, W. J.: Arterial Embolism.** New York State J. Med. 59: 2559, (July 1), 1959.

The origin and diagnosis of arterial embolism is reviewed. In 86.5 per cent of patients the source of emboli is said to be identifiable. The general management of the patient with acute arterial block includes the treatment of the basic disease, increasing the blood supply to the involved part, and the prevention of further extension of the blood clot already present. All modalities that act to achieve these results are in the medical treatment of these patients and should supplement surgical management in the operated patient. In certain situations, a delayed surgical approach utilizing a retrograde-flush technic might be beneficial. In general, life expectancy following one episode of arterial embolization is reduced to about one half of the normal expectancy because of subsequent emboli. Long-term anticoagulation is therefore indicated. Apparently cardiac atrial appendectomy adds no protection against subsequent embolism. Conversion of atrial fibrillation to sinus rhythm may be of value. The role of fibrinolysin in clot dissolution is still under investigation and when such agents with low toxicity are available, this type of therapy will probably be valuable.

KRAUSE

**Pendower, J. E. H.: Haematemesia from Rupture of Aneurysms into the Duodenum.** Lancet 1: 1165 (June 6), 1959.

Two cases are reported in which an aneurysm had ruptured into the duodenum causing death. One patient had multiple episodes of gastrointestinal bleeding for an arteriosclerotic aneurysm of the abdominal aorta that ruptured into the third part of the duodenum. In the other patient, multiple episodes of bleeding into the gastrointestinal tract was caused by a saccular aneurysm of the hepatic artery that ruptured into the first part of the duodenum. The literature is briefly reviewed.

SHEPS

**Pool, J. L.: Early Treatment of Ruptured Intracranial Aneurysms of the Circle of Willis with Special Clip Technique.** Bull. New York Acad. Med. 35: 357 (June), 1959.

Ruptured intracranial aneurysms were repaired

in 23 patients under hypothermia with the aid of temporary vascular clips. The mortality of 11.7 per cent for the entire group of 17 patients under the age of 50 compared favorably with mortality rates for untreated patients and for patients treated by other methods. The author concluded that early intracranial surgery was indicated preferably within 6 days after the presenting symptoms occurred and that satisfactory results could be expected in patients under 50 years of age in good physical condition but that results would be poorer in patients over the age of 50 and in those who were comatose, regardless of their age.

KARPMAN

**Prioleau, W. H., and Nunn, D. B.: Treatment of Venous Ulcers of the Leg: Review of 110 Operative Cases.** Ann. Surg. 149: 914 (June), 1959.

Two-hundred and seventeen patients with venous ulcer were followed for 10 to 15 years. Sufficient data for evaluation of the results were available in 110 patients who were operated upon. It was found that inspection and palpation of the extremity after the patient had been on his feet for some time was the best method of determining the status of the venous circulation. Tourniquet tests and venograms did not yield any significant information. The major factors in venostasis were noted to be the dilatating tortuous superficial veins and the incompetent communicating veins, the results of postphlebitic processes and primary varicose veins. Proper supportive measures were indispensable in the preparation of the leg for surgery and in prevention of recurrences. The Unna's boot remained the best method of accomplishing this support. The authors have discarded injection of sclerosing solution because, in their experience, it frequently resulted in uncontrolled thrombosis often affecting the deep veins. The surgical procedures used here were (1) limited vein excision with injections, (2) extensive vein excision through horizontal incisions, and (3) extensive vein excision with vertical incisions in the leg. In the first group there were 8 good results in 32 patients. In the second group there were 4 good results in 39 patients. In the third group there were 27 good results in 44 patients. The authors believe that the adoption of a vertical incision in the anteromedial aspect of the leg and at other sites as indicated makes possible a more thorough interruption of incompetent perforating veins and accounts for the better results in the third group. It is emphasized that all of these patients must continue to be observed for development of new incompetent perforating veins and varicosities.

LEVINSON

**Joss, J. P.: The Vascular Complications of Cervical Rib.** *Ann. Surg.* 150: 340 (Sept.), 1959.

The author points out that compression of the subclavian artery may occur at the site of callous formation after a fracture of the first rib as well as in the presence of a cervical rib. Fibrous bands may occasionally compress the artery but this is rare. He believes that the important alteration of physiology occurs in the poststenotic dilated segment of the vessel. This area is frequently the site of thrombus formation from which distal emboli may occur. In treatment, complete excision of the cervical rib as well as the adjoining prominence of the first rib are of paramount importance. In this author's experience, upper thoracic sympathectomy is preferred to excision of the dilated artery segment even if the latter is thrombosed. Where brachial plexus phenomena are found the difficulty is usually due to a short cervical rib with a fibrous band. Where vascular phenomena were not marked the subclavian artery was usually compressed between a cervical rib and a prominence on the first rib. Arteriograms still showed patent digital vessels in spite of ulcerations of fingers, so that diminished blood flow must be postulated instead of distal emboli as a cause for the finger ulcerations.

LEVINSON

**Sayre, G. P., and Campbell, D. C.: Multiple Peripheral Emboli in Atherosclerosis of the Aorta.** *Arch. Int. Med.* 103: 799 (May), 1959.

A case of multiple peripheral emboli from atherosclerosis of the aorta is reported with autopsy findings, and the pertinent literature is reviewed. The authors reemphasized the fact that multiple vascular occlusions of small arteries may occur from emboli broken loose from eroded atheromatous aortic plaques and that significant lesions may appear in the kidneys, brain, heart and extremities. The concomitant presence of a positive serologic test for syphilis or the presence of gout in these patients was believed to be fortuitous.

KRAUSE

## OTHER SUBJECTS

**Boe, G. K., and Abildskov, J. A.: Atrial Fibrillation as a Self-Sustaining Arrhythmia Independent of Focal Discharge.** *Am. Heart J.* 58: 59 (July), 1959.

Experiments in dogs are reported showing that atrial flutter induced either by electrical stimulation of the right atrium or by injection of pronitine into the atrial muscle disappeared when the inciting agent was eliminated, whereas atrial fibrillation could persist independent of the in-

citing agency. The independent survival of atrial fibrillation was found only in the presence of adequate cholinergic discharge. The various theories as to the mechanism of atrial fibrillation are discussed in terms of these experiments and it is concluded that irregular activation of the atria may be produced by (1) a single rapidly discharging ectopic focus, whether electrically or chemically induced, (2) multiple rapidly discharging foci, or (3) a rapidly circulating circus movement. It is further concluded that atrial fibrillation may be self-sustained and independent of the initiating agency provided that the atria are large enough (as the adult human atria are) or have a sufficiently brief refractory period.

SAGALL

**Blocker, T. G., Jr., Smith, J. R., Dunton, E. F., Protas, J. M., Cooley, R. M., Lewis, S. R., and Kirby, E. J.: Studies of Ulceration and Edema of the Lower Extremity by Lymphatic Cannulation.** *Ann. Surg.* 149: 884 (June), 1959.

The lymphatic drainage of the lower extremities was studied by cannulation in 65 patients and in 35 dogs. The lymphatic channels were visualized by the injection of radioactive iodinated serum albumin after cannulation. In addition, pressure determinations were made by electronic measurements. Investigations were performed on 25 normal patients and on 40 with various pathologic states, such as chronic edema, burns, chronic ulcerations, varicosities, involvement of lymphatics with infection, and metastatic malignancy. In the dog, the effects of hypoxia, trauma, and simulated altitude were studied. In the normal state the pressure findings were consistently subatmospheric and the channels appeared to be in the nature of potential spaces. Contrary to the usual concept, it was found that lymphatic channels from the foot did not converge to form larger vessels as they moved upward. Great variations were present because of congenital differences. Negative pressure in the lymphatics seemed to increase with motion and massage. In the presence of edema there was an increase in the size of capillary lymphatics. Edema, inflammation, mechanical blockage, and other pathologic states resulted in positive pressure readings. In chronic ulceration the obliteration of superficial lymphatics did not interfere with the lymph flow beneath the lesion unless congenital abnormalities existed. In the dog, lymphatic pressure became positive in the presence of trauma, hypoxia, and simulated increasing altitude. These studies indicate that this cannulation technique offers possibilities as a diagnostic, prognostic, and therapeutic tool, particularly in chronic edema and ulceration of the lower extremity.

LEVINSON

**Burnard, E. D.: Changes in Heart Size in the Dyspnoeic Newborn.** *Brit. M. J.* 1: 1495 (June 13), 1959.

The heart size in dyspnoeic premature babies was significantly greater for the first 3 days than in apparently healthy controls, and the decline in heart size by the fifth day was significant. In full-term babies the heart size was greater in the breathless babies in the first 30 hours than in normal subjects. Based on previous data these dyspnoeic babies also usually are found to have a crescendo systolic murmur and anomalous behavior of the heart rate. It is suggested, therefore, that the dyspnea in these babies is due to cardiac insufficiency and, furthermore, that there is usually an increase in the lung markings due to vascular congestion and edema. The author postulates asphyxia during birth as the mechanism for dyspnea in the full-term baby and in the premature child born without asphyxia. A defective respiratory mechanism is also presupposed.

KRAUSE

**Chapman, R. C., Kemp, V. E., and Taliaferro, I.: Pheochromocytoma Associated with Multiple Neurofibromatosis and Intracranial Hemangioma.** *Am. J. Med.* 26: 883 (June), 1959.

Three cases of pheochromocytoma associated with multiple neurofibromatosis are reported, which, in the authors' search, brings the reported cases of this combination to a total of 35. One other patient had this combination plus a cerebellar hemangioma. One additional patient also had Von Hippel-Landau's disease—one or more angiomatous malformations of the retina, each supplied by a dilated artery or vein. These lesions progress to form hemorrhages and exudates and finally lead to retinal detachment. Cystic hemangioblastoma of the cerebellum may also be found. Cystic lesions of the pancreas and kidney may occur. The authors conclude that the association of these familial disorders of the neurectoderm with pheochromocytoma is not only helpful in the clinical diagnosis of the pheochromocytoma, but strengthens the concept of the ectodermal origin of the related disorders.

RINZLER

**Dickinson, C. J., and Tomson, A. D.: Vertebral and Internal Carotid Arteries in Relation to Hypertension and Cerebrovascular Disease.** *Lancet* 2: 46 (July 18), 1959.

The flow rates through the internal carotid and vertebral arteries were determined in 61 cadavers. These were compared with a mean antemortem blood pressure. There was a negative correlation of high significance between flow in both vertebral arteries and blood pressure. The correlation

was greater than that for the flow in both internal carotid arteries and blood pressure. In addition, there was a definite relationship between total flow in all 4 major cervical arteries in the presence of spontaneous "strokes." The authors suggest that these results are compatible with the hypothesis that high blood pressure is an adaptation to restriction of flow in the vertebral arteries. Moreover, there is confirmation of the evidence that "caroticovertebral stenosis" may be the cause of most cases of cerebrovascular disease.

SHEPS

**Dickson, J. F., Homer, N. A. J., and Dow, J. W.: A System for Venoarterial Pumping.** *Surgery* 45: 288 (Feb.), 1959.

In potentially reversible cardiac lesions such as acute myocardial infarction, massive pulmonary embolism, and in some cases of congestive heart failure mechanical support of the circulation may be beneficial. The authors present a closed system for venoarterial pumping without oxygenation. The system was stable and non-traumatic and was suitable for prolonged use. The technique of use is described. Venoarterial pumping was performed for 52 hours in dogs with subsequent survival and for 26 hours in man.

KITCHELL

**Freeman, I., Jackson, D. A., and Collier, C. S.: Lactic Dehydrogenase Versus Glutamic Oxalacetic Acid Transaminase as a Diagnostic Test for Myocardial Infarction.** *Am. J. M. Sc.* 237: 768 (June), 1959.

Simultaneous determinations of the levels of serum glutamic oxalacetic acid transaminase and serum lactic dehydrogenase were made on 60 patients between 12 and 48 hours after the onset of the initial symptoms of acute myocardial infarction. These lesions were verified by serial electrocardiographic changes, necropsy evidence, and a classical history. All the patients exhibited elevated levels of transaminase, whereas only 35 patients had elevated levels of lactic dehydrogenase. The assay of transaminase would appear to be sufficiently superior to that of lactic dehydrogenase to confirm an impression of acute myocardial infarction between 12 and 48 hours of its occurrence.

SHEPS

**Hon, E. H.: The Fetal Heart Rate Patterns Preceding Death in Utero.** *Am. J. Obst. & Gynec.* 78: 47 (July), 1959.

The heart rate pattern of a 25-week fetus was studied prior to and during labor, until its death

in utero. An intrauterine electrode was placed directly on the fetus, and a continuous electrocardiographic tracing was recorded. The effects of uterine contractions, umbilical cord compression, and other procedures were discussed. Present clinical methods of determining fetal distress are often inaccurate. The fetal heart rate may return to "normal" after profound bradycardia following contraction or other manipulation of the umbilical cord. Thus a wait of 30 seconds after a contraction, before checking the heart rate, may cause a period of bradycardia to be missed. "Pathologic" bradycardia occurring many hours before death is described. The electrocardiographic pattern changed from a narrow U shape to become wider and deeper as the infant deteriorated and died. S-T segment depression was found to occur too late to have much clinical value as a sign of fetal distress.

MAXWELL

Hosler, R. M., Wolfe, K.: Closed-Chest Resuscitation. *Arch. Surg.* 79: 31 (July), 1959.

A variety of techniques were utilized to resuscitate dogs placed in ventricular fibrillation by an electrical current. Under ideal conditions—good oxygenation, sudden circulatory arrest, and light anesthesia—electrical countershock was effective when applied directly to the myocardium and also through the closed chest. When the breakdown of circulation was short, there was invariably a satisfactory return of blood pressure to normal and the electrocardiogram indicated a supraventricular rhythm. However, about 50 seconds appeared to be a dividing line between satisfactory and unsatisfactory defibrillation by external countershock. Beyond this time point, defibrillation could always be accomplished, as indicated by the electrocardiogram, but there was seldom a return of a satisfactory blood pressure or pulse. External stimulation (pacemaker) under the conditions of a cyanotic myocardium was apparently not too successful. Under these situations surgical exposure of the heart followed by a short manual pumping of the heart quickly and successfully restored the blood pressure to normal level. Another valuable procedure was the intraarterial brachial perfusion of epinephrine and dextrose solution under 200 mm. Hg pressure through a large bore needle. Oxygenated blood in place of all or a part of the dextrose solution was also efficacious. The heart that is found in a state of cardiac asystole could be reactivated to produce an effective circulation

by the intraarterial perfusion of 5 per cent dextrose and 1 or 2 mg. of epinephrine solution.

SHEPS

Miles, R. M.: Pheochromocytoma—Interesting Experiences with Three Cases. *Ann. Surg.* 149: 914 (June), 1959.

Three patients with pheochromocytoma are reported. The first 2 were unusual in that the presenting symptoms were those of gastrointestinal bleeding. In each of these patients thorough studies, including exploratory laparotomy in 1, revealed no evidence of any lesion of the gastrointestinal tract. It was believed that in these patients unusual rises of blood pressure resulted in rupture of small blood vessels within the gastrointestinal tract. In 1 of these patients pain in the left costovertebral angle was severe with attacks, and the pheochromocytoma was found in the left adrenal gland. In the third patient the tumor was found in the midabdomen between the vena cava and aorta, just below the level of the renal vein. It is pointed out that only 10 per cent of pheochromocytomas occur in an extra-adrenal location. A diagnosis of pheochromocytoma should be considered in paroxysmal hypertension, sustained hypertension with hypermetabolism or vasomotor episodes, children with hypertension in the absence of renal disease, and in patients showing an excessive response to histamine during gastric secretion tests. Adrenolytic or provocative drugs and the determination of urinary catechol amines are at present the best tests available for diagnosis. X-rays of the genitourinary and gastrointestinal tracts may be of value when the tumor is large. The risk of retroperitoneal pneumography is greater than that of exploratory laparotomy and less informative. It is pointed out that the transabdominal approach allows for exploration of both adrenal areas as well as the para- and prevertebral areas. Preparation with regitine prior to laparotomy is advisable to alleviate rise of blood pressure with manipulation of the tumor. Levophed is available to counteract hypotension in the immediate postoperative period. It is also well to have neosynephrine, adrenal cortical extract, and whole blood readily available. The importance of the surgical removal of these lesions is emphasized by the observation that approximately 800 deaths annually are due to pheochromocytoma. Most of these deaths are avoidable, if the diagnosis can be made.

LEVINSON

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## NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, N. Y.  
Telephone Gramercy 7-9170

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### AHA Scientific Sessions Program

Approximately 120 original scientific papers will be presented at the American Heart Association's 33rd annual Scientific Sessions to be held from Friday, October 21 through Sunday, October 23 at Kiel Auditorium, St. Louis. These presentations will be made during six sessions of broad clinical interest and at simultaneous Scientific Sessions under sponsorship of the Association's Councils which will be held throughout the three days.

In addition to hearing submitted papers on recent results of research, the six clinical programs will stress the application of new research knowledge during symposia, panels and lectures of general interest. The American Academy of General Practice has classified these sessions as acceptable for Category II credit for members.

An outline of the program follows:

#### **Friday, October 21:**

Introductory remarks by A. Carlton Ernste, M.D., President of the American Heart Association; Lewis A. Conner Memorial Lecture, "Physiology of the Circulation as Viewed by the Internist" by Eugene A. Stead, Jr., M.D., Professor and Chairman of Medicine, Duke University School of Medicine; joint program of AHA Council on Clinical Cardiology and American College of Cardiology; symposium on "Atrial Arrhythmias"; concurrent sessions on arteriosclerosis, rheumatic fever and congenital heart disease, and circulation; and a session for dentists.

On Friday evening, "Fireside Conferences" are scheduled under joint sponsorship with the American College of Cardiology. These will be held in the Sheraton-Jefferson Hotel.

#### **Saturday, October 22:**

Symposium on "Treatment of Curable Hypertension"; session on "Biophysical Methods in the Study of Circulation"; presentation of the Albert Lasker Award; George E. Brown Memorial Lecture, "Clinical Physiology of the Splanchnic Circulation," by Stanley E. Bradley, M.D., Professor of Medicine and Chairman of the Department, Columbia University College of Physicians and Surgeons; symposium on "Ventricular Septal Defects"; and morning and afternoon sessions for nurses.

#### **Sunday, October 23:**

Symposia on "Complete Heart Block"; "Nondietary Factors in Coronary Artery Disease"; and "Lipids and Arteriosclerosis"; panel on "Surgery for Extracranial Occlusive Cerebrovascular Disease"; and morning and afternoon sessions on cardiovascular films, each to be introduced and discussed by the author or other authority on the subject.

As in previous years, scientific and industrial exhibits will be on display in the Auditorium.

Registration and accommodation forms may now be obtained from the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

### AHA Annual Assembly Meeting

Following the AHA Scientific Sessions, the 35th Annual Meeting of the Assembly, delegate body of the American Heart Association, will begin on Monday, October 24 and continue through Tuesday, October 25 in St. Louis' Sheraton-Jefferson Hotel.

Seven Assembly Panels will convene all day Monday to discuss the following topics:

"Strengthening Relationships of Heart Associations," "Advancing the Research Program," "Advancing Physician Education," "Community Program Planning and Development," "Promoting the Rehabilitation Program," "Telling the Heart Story," and "Attracting and Keeping Volunteers."

The general session of the Assembly meets on Tuesday morning to review Panel recommendations and elect AHA officers and Board members.

The Association's Annual Dinner will be held Sunday evening, October 23 in the Sheraton-Jefferson Hotel.

#### **September 15 is Deadline to Submit AHA Fellowship Applications**

Applications for *Research Fellowships* and *Established Investigatorships* to be awarded by the Association for the fiscal year beginning July 1, 1961, must be submitted by September 15, 1960. The deadline for applying for Grants-in-Aid is November 1, 1960.

All applications must be made on forms available from the Assistant Medical Director for Research, American Heart Association, 44 East 23rd Street, New York 10, N. Y. Stipends, which have been increased to meet the rising cost of living, range as follows: *Established Investigators*, from \$7500-\$9900 plus departmental and dependency allowances; *Advanced Research Fellows*, from \$5500-\$6000 plus departmental and dependency allowances; *Research Fellows*, from \$4000-\$45000 plus dependency allowances. *Research Fellowships* are primarily awarded by local Heart Associations.

#### **\$5000 from Colorado Heart Group Supplements National Research**

The Colorado Heart Association has provided \$5000 to supplement the AHA national research support program for the 1960-61 fiscal period. The contribution was made in

partial support of a grant-in-aid to Colin H. M. Walker, M.D., Department of Pediatrics, University of Colorado Medical Center, to study the significance of serum mucoproteins and their composition and of the urinary hydroxyproline excretion in rheumatic fever.

Such contributions from local Heart Associations over amounts regularly assigned by them for national research permit support of additional investigations which could not otherwise be covered by the national research budget.

#### **Directory of Cardiovascular Films**

A Directory of Cardiovascular Films for use as a guide to clinicians, investigators, medical schools and others, has been compiled by the Association. The 106-page booklet lists 273 films on the cardiovascular system, describes them briefly and evaluates many of those listed. It also includes a list of film sources and subject and author indices. The Directory is available for \$1.00 from local Heart Associations or the American Heart Association, 44 East 23rd Street, New York 10, N. Y.

#### **Research Fellowships and Grants Offered by Life Insurance Fund**

The Life Insurance Medical Research Fund is now receiving applications for two types of awards to be available July 1, 1961, as follows:

(1) *Until October 15, 1960*, for postdoctoral research fellowships. Candidates may apply for support in any field of the medical sciences. Preference is given to those interested in fundamental problems, especially as related to cardiovascular function or disease. Minimum stipend \$4,500 with allowances for dependents and necessary travel.

(2) *Until November 1, 1960*, for grants to institutions in aid of cardiovascular research. Support is available for physiological, biochemical, and other basic work and clinical research in the cardiovascular field. Information and application forms may be obtained from the Fund's Scientific Director, 345 East 46th Street, New York 17, N. Y.

### Symposium on Heart Failure Begins AHA Monograph Series

A new monograph series of interest to physicians, investigators and students in the cardiovascular field has been inaugurated by the American Heart Association.

The first publication in the series, "Symposium on Congestive Heart Failure," edited by Herrman L. Blumgart, M.D., Editor-in-Chief of *Circulation*, brings together articles published originally in the January, February and March 1960 issues of *Circulation*.

The contents include: "Starling and the Concept of Heart Failure," Sir George Pickering; "Hemodynamic Aspects of Congestive Heart Failure," L. N. Katz, M. Feinberg and A. B. Shaffer; "Metabolism of the Heart in Failure," William H. Danforth, F. B. Ballard, K. Kako, J. D. Choudhury, and R. J. Bing; "Kidney in Congestive Heart Failure," A. C. Barger; "Unusual Causes of Heart Failure," Howard B. Burchell; "Clinical Management of Congestive Heart Failure," Herrman L. Blumgart and Paul M. Zoll; "Correction of Hyponatremia in Congestive Heart Failure," E. Hugh Luckey and Albert L. Rubin; "Clinical Consideration of Cor Pulmonale," Réjane M. Harvey and M. Irené Ferrer; "Pediatric Aspects of Congestive Heart Failure," Alexander S. Nadas and Anna J. Hauck; "Congestive Phenomena Occurring in Pregnant Women with Heart Disease," C. Sidney Burwell and James Metcalfe; and "Rehabilitation in Congestive Heart Failure," Howard A. Rusk and Menard M. Gertler.

Copies, at \$2 each, may be obtained by writing: Distribution Department, American Heart Association, 44 East 23rd Street, New York 10, N.Y.

A second monograph, "Symposium on Coronary Heart Disease," is scheduled for publication early in 1961.

### New Ballistocardiograph Society

The Society for Ballistocardiographic Research, recently founded with headquarters in Holland, welcomes members from the Eastern Hemisphere who are actively engaged in

research in this field. It is a sister organization to the Ballistocardiograph Research Society in Princeton, N.J., comprised of members from North and South America. Further information and copies of the proceedings of its First Congress may be obtained from Abraham Noordergraaf, Secretary, Bylhouwerstraat 6, Utrecht, Holland.

### Meetings Calendar

August 21-26: International Congress of Physical Medicine, Washington, D.C. W. J. Zeiter, 2020 E. 93rd St., Cleveland, Ohio.

August 28-September 3: International Society for Welfare of Cripples, 8th World Congress, New York. Donald V. Wilsoff, 701 First Ave., New York 17, N.Y.

September 1-7: International Congress of Nutrition, Washington, D.C. M. O. Lee, 9650 Wisconsin, Washington 14, D.C.

September 18-21: International Meeting of Forensic Pathology, New York. Milton Helpert, 55 East End Ave., New York 28, N.Y.

September 27-30: American Roentgen Ray Society, Atlantic City. Hugh Jones, 20 N. Wacker Drive, Chicago 6, Ill.

October 10-14: American College of Surgeons, Clinical Congress, San Francisco. W. E. Adams, 40 E. Erie St., Chicago 11, Ill.

October 21-23: American College of Cardiology, 9th Interim Meeting, St. Louis. Philip Reichert, American College of Cardiology, 350 Fifth Avenue, New York, N.Y.

October 21-25: American Heart Association, Annual Meeting and Scientific Sessions (October 21-23), St. Louis. American Heart Association, 44 East 23rd Street, New York 10, N.Y.

October 31-November 2: Association of American Medical Colleges, Hollywood Beach, Fla. Ward Darley, 2530 Ridge Ave., Evanston, Ill.

October 31-November 4: American Public Health Association, San Francisco. B. F. Mattison, 1790 Broadway, New York 19, N.Y.

November 28-December 2: American Medical Association, Clinical Meeting, Washington, D.C. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Ill.

November 30-December 3: Canadian Heart Association and National Heart Foundation of Canada, Toronto. J. B. Armstrong, 501 Yonge Street, Toronto 5, Canada.

### Abroad

August 14-20: Inter-American Congress of Cardiology (6th), Rio de Janeiro. Hugo Alquéres, Av. Nilo Pecanha, 38, Rio de Janeiro, Brazil.

August 24-27: International Congress of Internal Medicine, Basel, Switzerland. Secretariat, 13 Steinentorstrasse, Basel, Switzerland.

August 28-September 1: International Congress on Diseases of the Chest, Vienna. Murray Kornfeld, American College of Chest Physicians, 112 E. Chestnut Street, Chicago 11, Ill.

August 28-September 3: International Congress of Histochemistry and Cytochemistry, Paris. R. Weemann, 45 rue des Sainte-Peres, Paris 6e, France.

September 1-4: First International Congress of Nephrology, Geneva and Evian, France. G.

Richet, 149 Rue de Sevres, Paris 15, France.

September 4-10: International Society of Hematology, Tokyo. J. L. Tullis, 1180 Beacon Street, Brookline 46, Mass.

September 7-10: World Conference of Angiology, Bad Nauheim, Germany. Max Ratschov, Moserstrasse 1, Darmstadt, Germany.

September 18-25: European Congress of Cardiology, Rome. V. Puddu, Clinica Medica, University of Rome, Italy.

**1962:—October: Fourth World Congress of Cardiology, Mexico City. I. Chavez, Ave. Cuauhtemoc 300, Mexico, D.F.**

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